Deficits in dynamic gait stability as risk factors for falls in patients with multiple sclerosis

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1

The cost of managing patients with multiple sclerosis at Mafraq Hospital

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Background: Multiple sclerosis (MS) is a disabling life-long disease that manifests in different ways. Its associated costs and its economic impacts on young individuals have not been fully evaluated in the Middle East and North Africa (MENA) region. Various studies have been conducted globally to determine the causes, incidence, associated risk factors, and costs and its effect on people afflicted with MS.
Methods: A total of 109 patients with MS attending Mafraq Neurology clinic were involved in the study after approval from the Mafraq Research Ethics Committee. Data were collected retrospectively from the CERNER patient data base. Data included outpatient clinic visits, medications, hospital admissions, emergency department visits, magnetic resonance imaging (MRI) brain and spine, laboratory tests including (complete blood count (CBC), liver function tests (LFTs), vitamin D) from 2010 to 2017, and sick leaves for the year 2016.
Results: Patient's age ranged from 16 to 64 years with a mean of 34 years. A total of 26 nationalities were represented. Data were collected between 2010 and 2017 reporting on eight services. The mean cost for outpatient services was 683 AED. The mean cost for hospital admission was 131,265 AED. The mean cost for emergency visits was 704 AED. Brain MRIs had a mean of 1235 AED while spine MRIs had a mean cost of 1163 AED. The mean cost of medications was 93,980 AED. In 2016, the sick leaves had a mean cost of 7958 AED.
Conclusion: Our research shows that the management of patients with MS is highly costly, and this cost can even increase with time leading to a real economic burden. Further studies are needed to identify a solid plan to decrease the burden of this disease.

2

Practice of complementary and alternative medicine (CAM) among patients with multiple sclerosis in Eastern Region, Saudi Arabia

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Background: Little is known about the prevalence and practice of complementary and alternative medicine (CAM) among patients with multiple sclerosis (MS) in the Arab world. Studying CAM in Saudi population is important as it will reflect the influence of psychosocial, cultural, and religious factors on health beliefs and behaviors.
Objectives: The aim of this study was to determine knowledge and attitudes about CAM, prevalence of its use, reasons for its use, and types of CAM used in patients with MS in eastern province of Saudi Arabia.
Methods: This was a cross-sectional hospital-based study conducted in the MS clinic of King Fahd Hospital, Imam Abdulrahman Bin Faisal University. After obtaining informed consent to participate in the study, patients with MS were required to complete a questionnaire. Questionnaire includes questions divided into three categories: (1) demographic information, (2) specific characteristics of patient's disease, and (3) non-disease modifying drug (DMD) therapies used by patients (dietary interventions, such as vitamins and minerals, and special dietary pattern (i.e. goat milk, salt free, fat free) used for >3 months at least).
Results: A total of 100 patients from the MS clinic in King Fahd Hospital completed the survey. Of 100 patients, males were 35%, and females were 65%. Majority of patients were Saudi national (92%). Of 100, 4% were illiterate, 2% could read and write, 4% have primary education, 23% had secondary education, 54% were graduate, and 13% have completed post-graduation. Basic occupation was job in 51%, while 20% were jobless. Commonly used DMDs were interferon beta 1a in 68% of patients. Almost half of the patients had more than attacks in the past year (47%). Majority of patients had history of CAM use (99%), and the main reason to use CAM was a feeling of participation in management in 43%, followed by successful stories from other patients in 28%, getting recommendations from others in 17%, and 12% felt that DMDs are not working properly. The most common CAM was prayers in 34%, followed by dietary medicines in the form of vitamins, minerals, and special dietary patterns in 27%, Hejama in 20%, and mind–body medicine in 17%. Majority of patients (52%) got the knowledge of CAM through social media.
Conclusion: CAM treatments were largely used by patients with MS in eastern province of Saudi Arabia. In view of the common belief that CAM has fewer side effects than conventional medicine, neurologists need to increase their awareness of CAM.

3

Developing multiple sclerosis in Bernard–Soulier syndrome patient

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Background: Bernard-–Soulier syndrome (B-SS) is a rare inherited bleeding disorder caused by abnormal platelets and subsequent abnormal clotting.
Methods: We report on a patient diagnosed with multiple sclerosis (MS) and B-SS.
Results: A 36-year-old female was admitted to our hospital complaining of gait unsteadiness and imbalance and slurred speech.

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She was diagnosed with B-SS 11 years prior to presentation. Her brain magnetic resonance imaging (MRI) revealed hyperintense lesions in the cerebellar peduncle, periventricular demyelinating lesions in T2, and fluid attenuated inversion recovery (FLAIR) suggestive of MS Moreover, her cervical MRI revealed one hyperintense demyelinating lesion. Her lumbar puncture showed positive oligoclonal bands. She was diagnosed with secondary progressive MS.
Conclusion: Coexistence of the two diseases has not yet been described in the literature. Further studies are needed to clarify this issue.

4

Vitamin D and multiple sclerosis in a cohort of Algerian patient

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Background: The risk of multiple sclerosis (MS) is determined by genetic and environmental factors. One of the latter is vitamin D deficiency, which has attracted attention in the last decade. Our objective was to evaluate serum 25 hydroxyvitamin D (25-OH D) levels in patients with MS and determine whether this rate correlated with the clinical characteristics of the disease.
Methods: We conducted a prospective study between January 2016 and June 2017 during which serum 25-OH D levels were obtained from patients with MS. A serum level of 25-OH D >30 ng/mL was considered normal and a level between 30 and 10 ng/mL was defined as vitamin D deficiency. Severe deficiency was defined at <10 ng/mL.
Results: In all, 143 patients with MS were included in the study. The serum level of vitamin D was collapsed in a high proportion of our patients (67%). There is no correlation between the 25-OH D level and the annualized rate of the previous year in patients with relapsing–remitting MS (RRMS). High Expanded Disability Status Scale (EDSS) scores correlated with low vitamin D levels.
Conclusion: Any hypovitaminosis D should be corrected in patients with MS, and long-term evaluation is necessary in order to assess the impact of this supplementation on long-term disease progression.

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Pediatric multiple sclerosis in a cohort of Algerian patient

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Background: Multiple sclerosis (MS) is a disease of young adults, but its onset in childhood is frequently observed. Recently, several networks are collaborating to advance the management of this disease in the pediatric population.
Objectives: To describe the clinical and paraclinical characteristics of a pediatric MS population; to assess the response to different treatments; and to describe the evolution of the disease.
Methods: This is a retrospective study of patients aged less than 18 years who were diagnosed with MS according to 2010 McDonald's criteria.
Results: In all, 25 pediatric MS patients were included. The mean age was 15 ± 4.38 years. Most of the patients (76.6%) had a mono symptomatic onset. Baseline brain magnetic resonance imaging (MRI) showed periventricular lesions in 91% of the patients and cerebellum and corpus callosum lesions in 38% and 36% of the cases, respectively. A total of 87.5% of the patients were diagnosed with relapsing–remitting MS. About 76% of the patients were treated with interferons while 9.5% were maintained on monthly natalizumab infusion. Their baseline Expanded Disability Status Scale (EDSS) ranged between 4 and 6 in 28.5% of the patients and greater than 6 in 19%. The median time to reach EDSS 6 in our cohort was 8.27–10.68 years compared to 12.17–13.24 years in the adult population.
Conclusion: In pediatric MS, functional and cognitive dysfunction can interfere with academic achievement. Early treatment is highly recommended to improve the quality of life of young patients.

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Body size and the risk of multiple sclerosis in Saudi Arabia, case–control study, 2016

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Background: Overweight/obesity may increase risk of multiple sclerosis (MS).
Objective: To determine whether body size during different age periods is associated with an increase in MS risk in Saudi Arabia.
Methods: In all, 307 MS cases and 307 healthy controls were selected from MS clinics and wards in three main cities in different regions in KSA. Participants selected their body size by choosing a silhouette 1–9 during different age periods. Odds ratio (OR) and 95% confidence intervals (CIs) were calculated. Logistic regression models were adjusted for potential confounding factors.
Results: A large body size 6–9 and body size 5 during intermediate school level increase risk of MS (adjusted OR (AOR): 3.74, 95% CI: 1.39–10.04 and AOR: 2.41, 95% CI: 1.01–5.75, respectively), while being with smallest body size (1) during intermediate school decreases risk of MS (AOR: 0.28, 95% CI: 0.13–0.61).
Conclusion: Overweight and obesity during intermediate school level were associated with increased risk of MS.

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Environmental exposures and the risk of multiple sclerosis (MS) in Saudi Arabia (KSA), 2016

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Background: Multiple sclerosis (MS) is one of the disabling chronic diseases affecting adults. The risk factors are not yet known in KSA, while the prevalence of MS is rising. The goal of the study was to determine the association between environmental exposures among patients with MS.
Methods: In all, 307 MS cases and 307 healthy controls were selected from MS clinics and wards in three main cities. Information on demographics, family history of MS, medical and family history, sun exposure, obesity at different age periods, tobacco use, diets, consanguinity role, and coffee consumption was obtained from self administered questionnaire (SAQ). Logistic regression (LR) models were adjusted for potential confounding factors.
Results: Mean age was 33 years and 76% were female. The multivariate (MV) analysis showed that being the first birth order position (odds ratio (OR): 1.79; 95% confidence interval (CI): 1.11–2.88), having measles (OR: 3.11; 95% CI: 1.76–5.5), having a large body size at primary school level (OR: 4.35; 95% CI: 1.20–15.84), eating from restaurant ≥5 times/week (OR: 2.14; 95% CI: 1.11–4.13), and having a family history of MS (OR: 6.25; 95% CI: 3.09–12.62) were independently associated with increased risk of MS. Eating ≥5 servings of fruit/week (OR: 0.31; 95% CI: 0.20–0.47), having a high sun exposure at primary school level (OR: 0.58; 95% CI: 0.37–0.91), and also having a high sun exposure at university school level (OR: 0.50; 95% CI: 0.30–0.84) were independently associated with decreased risk of MS.
Conclusion: Our study suggests a protective role of high sun exposure and consumption of fruits during primary and university school levels. Obesity during primary school level is associated with increased risk of MS. Encouragement of outdoor activity and healthy diet at school level especially for females is highly suggested.

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Cardiovascular abnormalities in patients with relapsing–remitting multiple sclerosis

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Background: Autonomic dysfunction is a prevalent but frequently overlooked symptom among patients with multiple sclerosis (MS). It can be explained by lesions within central nervous system (CNS) involving areas responsible for autonomic regulation. Impairment of cardiovascular (CV) autonomic reflexes has been described in multiple sclerosis (MS), and believed reflecting dysfunction of reflex pathways located within the CNS. Our objectives were to detect the cardiovascular disturbances in patients with relapsing–remitting MS (RRMS) and to correlate the location of the brain lesions with such disturbances.
Methods: Forty-eight patients with RRMS, according to revised McDonald's criteria (2010), and 25 healthy control subjects were included. Evaluation of the CV functions in both groups was carried out via symptom analysis, assessment of blood pressure (BP) in response to change in posture, electrophysiological studies for heart rate variability (HRV) testing using 24-hour HR recording by halter electrocardiography (ECG), and R-R interval variation in response to normal and deep breathing, valsalva maneuver, and standing.
Results: Postural hypotension was reported in 41% of patients with RRMS, having both symptoms of orthostatic dizziness and decrease in systolic BP (SBP) and/or diastolic BP with a mean of 25 ± 11 mmHg for SBP and 10 ± 4 mmHg for diastolic BP. Changes in heart rate after deep breathing were evident in 54.3% which showed an increase or decrease in HR of less than 10 beats/min with significant difference when compared to controls ($p = 0.04$). Whereas no significant difference was found in the R-R interval variability test between patients and controls with normal breathing, valsalva maneuver, and standing up ($p = 0.17$; 29; 0.39 respectively). Patients having pericallosal plaques had a significant difference in the mean change in SBP on standing compared to those without such lesions ($p = 0.04$). However, no significant correlation was detected between the CV symptoms and the duration of the disease, total number of relapses, or the disability progression.
Conclusion: Autonomic dysfunction is not uncommon in patients with RRMS including CV reflexes' dysfunction which should be identified to allow proper symptomatic management.

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Epidemiological data of patients with multiple sclerosis

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Background: Multiple sclerosis (MS) is a demyelinating disease of the central nervous system, of undefined etiology, so epidemiological studies are fundamental.
Objectives: To portray epidemiological characteristics in patients with MS.
Methods: Data collection of 600 epidemiological questionnaires sent by mail, by a Civil Social Institution, in São Paulo, Brazil, to patients with MS.
Results: A total of 177 people were randomly selected from a sample of 600 patients with MS between 2006 and 2010. A total of 65% of them were from São Paulo, 70% were women, 55% were married, 76% were white, and 41% had a high school diploma and 40% had a university diploma. The majority of them were born in the 1970s, with the oldest being born in 1938 and the youngest in 1997. Only 24% were working. As for the symptoms, 66% of the patients presented with muscle weakness, 57% with fatigue, 79% with numbness, and 56% with imbalance. The psychiatric symptoms observed were mood disorders in 51% of the cohort. Most of the patients performed cervico-dorsal and brain magnetic resonance imaging (MRI) and 55% of them were maintained on interferon.
Conclusion: The majority of our cohort were predominately female who were born in 1970s. Most of them are not working due to physical and psychological symptoms.

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Quality-of-life evaluation with MSQOL-54, of patients with multiple sclerosis

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Background: Multiple sclerosis (MS) is a degenerative and chronic disease that causes physical and cognitive disorders leading to changes in quality of life.
Objectives: To evaluate patient's perception of his physical and mental quality of life.
Methods: Patients with MS were evaluated, through MSQOL-54, in Civil Social Institution, in São Paulo, Brazil.
Results: A total of 35 people (11 men and 24 women) were assessed. The predominant age group was between 40 and 60 years (63.1%) with a mean age of 44.49 years and standard deviation (SD) of 11.34 years; 42.9% were married; 21% were retired and unemployed; and 74.3% had a high level of education. A total of 40% were diagnosed 10–20 years ago: 82.9% had relapsing–remitting MS (RRMS); 74.3% had an Expanded Disability Status Scale (EDSS) up to 3.5; 94.3% had at least one relapse and 65.2% had no relapses in the last 2 years. About 91.4% received treatment; 28.6% were maintained on interferon therapy and 40% were taking vitamin D supplement in addition to their disease-modifying therapy. A total of 62.9% complained of motor problems but did not use assistive devices for ambulation; 74.3% had visual problems and 28.6% suffered from cognitive problems mainly attention disorder; 40% had urinary problems; and 22.9% complained of insomnia. As for fatigue, 54.3% had mental fatigue, 88.6% physical fatigue and 45.7% visual fatigue. About 84.1% scored above average in general health perception (mean 63.36) and 75.4% were above average in mental health (mean 55.98) in MSQOL-54.
Conclusion: We concluded that the perception about the physical and mental quality of life is above average, with the perception of physical health being greater than that of mental health.

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Long-term lymphocyte counts in patients with RRMS treated with cladribine tablets

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Background: Cladribine tablets' (CTs) efficacy was demonstrated in the CLARITY study. Lymphopenia was the most commonly reported adverse event (AE), consistent with CT's mechanism of action. Absolute lymphocyte counts (ALCs) were investigated to 312 weeks and B- and T-cell subsets to 240 weeks after the first administered CT dose, in patients with relapsing–remitting MS (RRMS) receiving two annual courses of CT (3.5 mg/kg cumulative dose) followed by no further active treatment.
Methods: Data from patients randomized to CT in CLARITY/CLARITY Extension including time in the PREMIERE registry ($N = 685$) were pooled. Median cell counts are reported.
Results: Baseline ALC was 1.86×10^9/L. During Year (Y)1, ALC reached nadir at Week (Wk) 9 (1.00×10^9/L) and then gradually increased. During Y2, ALC reached nadir at Wk55 (0.81×10^9/L) and recovered to normal ($\geq 1.00 \times 10^9$/L) by the end of Y2 (Wk96), continuing to increase thereafter. ALC returned to normal in 75% of patients by Wk144. Baseline CD4+ was 851 cells/μL. After treatment in Y1, CD4+ reached nadir at Wk16 (385 cells/μL) and then gradually increased. CD4+ reached nadir after Y2 treatment at Wk60 (292 cells/μL). Values reached the 350 cells/μL threshold by approximately Wk120, continuing to improve thereafter. Baseline CD8+ was 378 cells/μL. CD8+ reached Y1 nadir at Wk16 (239 cells/μL) and then gradually increased; Y2 nadir was reached at Wk72 (232 cells/μL). CD8+ recovered quickly after treatment and never decreased below the 200 cells/μL threshold. Baseline CD19+ was 205 cells/μL. After Y1 treatment, CD19+ reached nadir at Wk9 (18 cells/μL) and after Y2 treatment at Wk52 (31 cells/μL). CD19+ then gradually recovered, reaching the 100 cells/μL threshold by Wk96, continuing to improve thereafter.
Conclusion: Lymphocyte recovery begins soon after CT treatment, with ALC, CD19+ B cells and CD4+ T cells reaching threshold values by 7.5, 12 and 18 months, respectively, after the last dose in Y2. CD8+ cells never decreased below the threshold.

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Analysis of relapse rates and relapse-free patients in the CLARITY and CLARITY Extension studies

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Background: In CLARITY, giving cladribine tablet (CT) annually for 2 years significantly reduced relapse rates and disability progression versus placebo (PBO). Here, the efficacy of 2 year's additional treatment with CTs or PBO in patients with relapsing multiple sclerosis (RMS) was assessed in an extension (EXT) to the CLARITY study.
Methods: In CLARITY-EXT, patients who had received PBO in CLARITY were assigned to CT 3.5 mg/kg body weight; those who received CT (3.5 or 5.25 mg/kg) in CLARITY were re-randomised (2:1) to CT 3.5 mg/kg or PBO. Annualised relapse rates (ARRs) and proportions of patients qualifying relapse free were compared at different times (i.e. CLARITY and CLARITY-EXT) within the following groups: patients treated with CT 3.5 mg/kg in CLARITY and PBO in CLARITY-EXT ($n = 98$); CT 3.5 mg/kg in CLARITY and CT 3.5 mg/kg in CLARITY-EXT ($n = 186$); CT 5.25 mg/kg in CLARITY and CT 3.5 mg/kg in CLARITY-EXT ($n = 186$); PBO in CLARITY and CT 3.5 mg/kg in CLARITY-EXT ($n = 244$).

Results: No significant differences in ARR were seen between CLARITY and CLARITY-EXT except in patients who received PBO in CLARITY and CT 3.5 mg/kg in CLARITY-EXT (0.26 vs 0.10, $p < 0.0001$). In CLARITY-EXT, >70% of patients qualified relapse free in each group with no significant differences seen between CLARITY and CLARITY-EXT except in patients treated with PBO in CLARITY and CT 3.5 mg/kg in CLARITY-EXT (58.0% vs 79.6%, $p < 0.0001$).
Conclusion: Comparing CLARITY with CLARITY-EXT demonstrates that CT produced durable clinical benefits: patients who received CT in CLARITY and PBO in CLARITY-EXT maintained low relapse rates throughout. Patients who received CT in CLARITY and CT in CLARITY-EXT showed no additional benefit versus CT treatment in CLARITY only. For patients who received PBO in CLARITY, switching to CT in CLARITY-EXT significantly reduced ARR and increased the proportion of relapse-free patients.

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Cladribine tablets in the ORACLE-MS study open-label maintenance period: Analysis of efficacy in patients after conversion to clinically definite multiple sclerosis (CDMS)

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Background: In the ORACLE-MS study in patients with a first demyelinating attack, cladribine tablets (CTs; 3.5 and 5.25 mg/kg) significantly reduced the risk of conversion to clinically definite multiple sclerosis (CDMS) compared with placebo. If CDMS occurred in the double-blind, initial treatment period (ITP), patients were treated with subcutaneous (SC) interferon-beta-1a in an open-label maintenance period (OLMP).
Methods: Participation in the ORACLE-MS OLMP was dependent on the clinical course of the patient's disease in the ITP. Patients in ORACLE-MS who converted to CDMS during the ITP entered the OLMP and were treated with SC interferon-beta-1a (titrated over 4 weeks up to the dose of 44 μg) administered three times per week. Annualised relapse rate (ARR) was assessed during ORACLE-MS OLMP, in patients randomised to CTs 3.5 and 5.25 mg/kg, or placebo, in the ITP.
Results: In all, 109 patients in ORACLE-MS converted to CDMS in ITP and received at least one dose of interferon-beta-1a. The median time on interferon-beta-1a was 56.0 weeks. Estimated ARRs in the OLMP were 0.14 (95% confidence interval (CI): 0.00–0.27) for patients ($n = 25$) originally treated with CT 3.5 mg/kg; 0.24 (95% CI: 0.07–0.40) for patients ($n = 24$) originally treated with CT 5.25 mg/kg and 0.42 (95% CI: 0.28–0.56) for patients ($n = 60$) who originally received placebo in the ITP.
Conclusion: A treatment effect versus placebo of CTs given in ITP continues to be observed in patients who convert to CDMS and switch to treatment with SC interferon-beta-1a. Patients who had been treated with CTs and who had converted to MS during ORACLE-MS ITP had lower ARR during the OLMP, relative to those patients who had received placebo during ORACLE-MS ITP.

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Cladribine tablets for treatment of patients with multiple sclerosis (MS): Integrated analysis of safety from the MS clinical development program

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Background: The efficacy of cladribine tablets (CTs) for early multiple sclerosis and relapsing MS (RMS) has been shown in ORACLE-MS, CLARITY, and CLARITY Extension. Adverse events (AEs) from these studies have been reported separately. Here, we report a pooled integrated safety analysis of CT's AE profile from trials which evaluated CT 3.5 mg/kg (CT3.5) as monotherapy in patients with early MS or RMS.
Methods: The CT3.5 cohort comprised 923 patients (3432.65 patient-years (PY) exposure) derived from CLARITY, CLARITY Extension, ORACLE-MS, and the PREMIERE registry; the placebo cohort comprised 641 patients (2025.97 PY).
Results: The mean study period for patients receiving CT3.5 was 194 weeks and 165 weeks for placebo recipients. Adjusted AE (Adj-AE) per 100 PY rates for CT3.5 and placebo, respectively, were treatment emergent AE (TEAE), 103.3 and 94.3; TEAEs leading to discontinuation, 2.1 and 1.1; serious AEs, 4.0 and 3.6; serious AEs leading to death, 0.26 and 0.25. Regarding known events expected with CT treatment, Adj-AE per 100 PY for lymphopenia were 7.94 (CT3.5) and 1.06 (placebo); for system organ class of infection and infestations, 24.93 (CT3.5) and 27.05 (placebo); herpes zoster, 0.83 (CT3.5) and 0.20 (placebo). Adj-AE per 100 PY for the system organ class of neoplasms, benign, malignant, and unspecified was 1.14 and 1.01, for CT3.5 and placebo, respectively.
Conclusion: The AE profile for CT3.5 as monotherapy has been well-characterized in a pooled population of patients with early MS and active RMS. Lymphopenia was expected from CTs' mode of action; herpes zoster was reported more frequently in patients experiencing Grade 3 or 4 lymphopenia; no clustering of types of malignancy was seen, and no malignancies commonly associated with immunosuppression were observed.

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Efficacy of cladribine tablets 3.5 mg/kg in high disease activity (HDA) subgroups of patients with relapsing multiple sclerosis (RMS) in the CLARITY study

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Background: In the CLARITY study, treatment with cladribine tablets (CTs) showed strong efficacy versus placebo in a large cohort of patients with relapsing multiple sclerosis (RMS) over 2 years. Patients with high disease activity (had) are at higher risk of relapses and disability progression. Here, the effects of CT 3.5 mg/kg (CT3.5) versus placebo were compared in subgroups of CLARITY patients selected using two HDA definitions.

Methods: CLARITY patients randomised to CT3.5 ($N = 433$) or placebo ($N = 437$) were retrospectively analysed using two different HDA definitions based on relapse history, prior treatment and magnetic resonance imaging (MRI) characteristics. Patients were categorised according to whether they had experienced high relapse activity (HRA; ≥2 relapses in the previous year) regardless of prior treatment, or HRA plus treatment nonresponse (HRA + TNR; ≥2 relapses in the previous year, or ≥1 relapse in previous year while on disease modifying drug (DMD) therapy and ≥1 T1 Gd+ or ≥9 T2 lesions).

Results: In the overall CLARITY population, CT3.5 reduced the risk of 6-month confirmed Expanded Disability Status Scale (EDSS) progression versus placebo (hazards ratio (HR) = 0.53, 95% CI: 0.36–0.79). A larger risk reduction for CT3.5 versus placebo was seen (HR = 0.18 each, 95% CI: 0.08–0.44 and 0.07–0.43) in the HRA subgroup ($p = 0.0036$ nominal significance vs non-HRA) and the HRA + TNR subgroup ($p = 0.0037$ significance vs non-HRA+TNR), indicating greater responsiveness to CT3.5 in patients identified by these criteria. Similar patterns were observed for time to 3-month EDSS progression. ARR was lower with CT3.5 than placebo in the overall population (relative risk (RR) = 0.42, 95% CI: 0.33–0.52), and even lower with HRA (RR = 0.32, 95% CI: 0.22–0.47) and HRA + TNR (RR = 0.33, 95% CI: 0.23–0.48; each $p < 0.0001$ vs placebo). Strong treatment effects on radiological markers were observed in each HDA subgroup.

Conclusion: In CLARITY, patients identified by HDA criteria showed clinical and MRI responses to CT3.5 that were generally better than, or at least comparable with, the overall CLARITY population.

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Cladribine tablets produce selective and discontinuous reduction in B and T lymphocytes and natural killer cells in patients with early and relapsing multiple sclerosis (ORACLE-MS, CLARITY and CLARITY extension)

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Background: Efficacy of cladribine tablets (CTs) was demonstrated in patients with early multiple sclerosis (MS) (ORACLE-MS) and relapsing–remitting MS (RRMS) (CLARITY/Extension). We evaluate the effect on B, T and natural killer (NK) cell profiles after CT administration.

Methods: Longitudinal evaluation of peripheral blood lymphocyte subtypes was conducted for patients receiving the first course of CT either from the initial 3.5 mg/kg active treatment groups (ORACLE-MS and CLARITY) or the placebo-switched-to-active-treatment groups (CLARITY Extension). Lymphocytes were immunophenotyped at baseline and Weeks 5, 13, 24 and 48. Changes in cell numbers and composition of lymphocyte subtypes were evaluated.

Results: Temporal profiles of CD19+ B lymphocytes and CD4+ and CD8+ T lymphocytes were generally consistent across studies. The fastest cell reduction occurred with CD19+ B cells (approximately 75% at Week 5 in each study). CD19+ B-cell nadir occurred at Week 13 with 81%, 84% and 82% median reductions for patients receiving CT in CLARITY ($N = 97$), CLARITY Extension ($N = 136$) and ORACLE-MS ($N = 41$), respectively. Reconstitution of CD19+ B cells towards baseline occurred from Week 24 to 48. CD4+ and CD8+ T cells were also markedly reduced, but less than CD19+ B cells (at most 55% at Week 13 for CD4+ cells and 48% at Week 48 for CD8+ cells in patients treated with CT in ORACLE-MS). Reductions in T cells were discontinuous but had not fully returned to baseline by Week 48. CD16+/CD56+ NK cells were also transiently reduced; nadir occurred at Week 13 in ORACLE-MS (44% reduction), with recovery at Weeks 24 (29% reduction) and 48 (23% reduction).

Conclusion: CT achieved an early and discontinuous reduction in B cells with rapid reconstitution to baseline, and a moderate and discontinuous reduction in T cells. There were early decreases in NK cells followed by rapid recovery.

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Efficacy of cladribine tablets in patients with relapsing–remitting multiple sclerosis (RRMS) in the 120-week extension to the CLARITY study

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Background: Cladribine tablets (CTs), given annually for 2 years in short-duration courses in CLARITY, significantly improved clinical (relapses and disability progression) and magnetic resonance imaging (MRI) outcomes. After a variable treatment gap (median 40 weeks), 2 additional years of CT treatment versus placebo were assessed in CLARITY-Extension (EXT). This analysis assessed the efficacy of CT in patients with relapsing–remitting multiple sclerosis (RRMS) treated for 2 additional years beyond the initial 2 years (CLARITY).
Methods: In CLARITY, patients were randomized to treatment with placebo or CT (3.5 or 5.25 mg/kg bodyweight). In CLARITY-EXT, placebo recipients in CLARITY received CT3.5 mg/kg; cladribine recipients were re-randomized 2:1 to CT3.5 mg/kg or placebo (five groups in total). This allowed comparison of 2 years-only treatment plus ≥2 years follow-up versus 4 years' treatment. Clinical assessments included annualized relapse rate (ARR) and disability score.
Results: Baseline characteristics were similar across groups, although placebo recipients in CLARITY showed evidence of greater clinical and magnetic resonance imaging (MRI) disease activity. In groups treated with CT in CLARITY, efficacy was maintained in CLARITY-EXT; 2 years' additional CT treatment was associated with a slight incremental benefit. ARR in patients treated with CT3.5 mg/kg in CLARITY and placebo in CLARITY-EXT was 0.15 (97.5% confidence interval (CI): 0.09–0.21; $n = 98$); in patients treated with CT3.5 mg/kg in both CLARITY and CLARITY-EXT, ARR was 0.10 (97.5% CI: 0.06–0.13; $n = 186$, $p = 0.059$). Both groups showed comparable proportions of relapse-free patients (75.6% and 81.2%, respectively) and time-to-first relapse (vs first dose in CLARITY). Median Expanded Disability Status Scale (EDSS) scores were comparable across all groups; no significant between-group differences were seen in time to confirmed 3-month EDSS progression in CLARITY-EXT.
Conclusion: CLARITY-EXT demonstrated that in a majority of patients, the clinical benefits of CT3.5 mg/kg given in Years 1 and 2 may be maintained for ≥4 years, with decisions on further treatment based on monitoring during this period.

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If initial repeated neuromyelitis optica antibody is negative, do we still consider neuromyelitis optica spectrum disorder?

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Background: To present a case of long extensive transverse myelitis and postrema syndrome with a persistent negative neuromyelitis optica (NMO) antibody for 2 years which later became positive.
Case history: This is the case of a 40-year-old Indian lady who presented with history of acute progressive paraparesis in May 2015. Her cervico-dorsal magnetic resonance imaging (MRI) showed a long extensive demyelinating lesion at the level of T2–T10. She received a pulse of methylprednisolone for 5 days but she did not improve. Therefore, she underwent five sessions of plasmapheresis. Her lumbar puncture showed a high white blood cell (WBC) 166, cerebrospinal fluid (CSF) protein of 1.2 g/dL, and positive oligoclonal bands. Cytology and acid-fast bacillus (AFB) polymerase chain reaction (PCR) were negative. Anti-nuclear antibody (ANA) was 1:320. NMO antibody performed upon presentation and repeated after 6 weeks, 3 months and 12 months was negative. Anti-myelin oligodendrocyte glycoprotein (MOG) antibody was also negative. She gradually improved and remained stable until February 2017 when she experienced intractable vomiting. Her MRI showed a demyelinating lesion in the postrema region. She a pulse of methylprednisolone for 5 days after which she recovered well. She travelled to the United States and repeated her NMO antibody test there which became positive. She was started on rituximab infusions every 6 months. Since then, she was clinically and radiologically stable on rituximab.
Conclusion: In typical NMO spectrum disorder (NMOSD), NMO antibody can still be negative initially. Corticosteroid treatment, plasmapheresis, or testing method could falsely affect the result. Thus, high clinical suspicion is required in NMOSD-suspected cases even when antibody is negative.

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Characterisation of novel anti-neuronal antibodies in multiple sclerosis

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Background: Grey matter pathology is extensive in relapsing–remitting and secondary progressive multiple sclerosis (MS) and has been shown to correlate with disability. Histo-pathological studies demonstrate neuronal loss correlates strongly with reduction in cerebral volume. We previously identified novel anti-neuronal antibodies in MS.
Objective: To describe the characteristics of novel anti-neuronal antibodies in MS.
Methods: In all, 79 patients with relapsing–remitting MS and 61 healthy blood donors were analysed. Sera were applied to frozen cryostat sections of rat cortex, cerebellum, kidney and small intestine that had been fixed using in vitro 2% paraformaldehyde perfusion. Bound IgG was detected using a goat anti-human IgG (Alexa Fluor 488) and M1 Zeiss Axiocam Imager. Specimens were analysed by two raters in a blinded fashion for binding to neurons and other central nervous system (CNS) structures and regarded as positive if fluorescence was greater than ++ which equivocated to an antibody dilution of more than 1:320.
Results: Anti-neuronal antibodies were more frequently detected in MS (35.4%, 28/79) than healthy controls (11.5%, 7/61, $p < 0.05$). Antibodies directed against neuronal cytoplasm were most frequent in MS (20.3%, 16/79) and usually involved cortical

neurons and cerebellar Purkinje cells although the pattern varied widely. An antibody directed against a vesicular intracytoplasmic component of interneurons (bipolar cells, Golgi, and basket cells) was found in 10.1% of patients with MS. Antibodies were also identified against synaptic vesicles, neurofilaments and neuronal nuclei.

Conclusion: Anti-neuronal antibodies are more frequent in MS than healthy people and have a wide distribution of targets. The heterogeneity of this response may imply epitope spreading and "bystander" immune responses although this needs further evaluation for each of the numerous novel antibodies identified in this study.

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Deficits in dynamic gait stability as risk factors for falls in patients with multiple sclerosis: A prospective cohort study

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Background: Falls while walking are frequent in patients with multiple sclerosis (MS). The physical impacts of falls can cause activity limitations and may have significant effects on patient's participation in the society. Therefore, an early gait stability index would be useful to identify patients at high risk of falling and to prevent the occurrence of future falls. Derived from chaos theory, local dynamic stability, defined by the maximal Lyapunov exponent (LyE), assesses the sensitivity of a dynamic system to small perturbations and has been found to be associated with falling in the older adults. However, in patients with MS, this relationship has not been investigated previously. Therefore, the aim of this study was to prospectively investigate deficits in local dynamic stability as risk factors for falls in patients with MS.

Methods: Seventy patients with MS were assessed under two experimental conditions, including (1) normal walking and (2) normal walking with cognitive task (aloud backward counting). Kinematic data were collected using a seven-camera motion capture system while patients walked on a treadmill. A cluster of three infrared retro-reflective markers were placed over the level of T7 to calculate local stability. Participants were classified as none-fallers and fallers (≥1) based on their prospective fall occurrence.

Results: In this study, 42 (49%) participants recorded one or more falls and were classified as fallers. The results of logistic regression analysis revealed that LyE under both single ($p < 0.01$, odds ratio (OR) = 2.125 (1.230–3.671) and dual task ($p < 0.05$, OR = 1.689 (1.09–2.837)) conditions was able to significantly predict falls in patients with MS.

Conclusion: The results of this study can be used by clinicians to identify potential fallers in patients with MS. Moreover, assessment of gait stability deficits and identification of more risk factors for falls in patients with MS can provide a background for development of perturbation-based rehabilitation programs for fall prevention.

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Anti-JCV antibody sero-positivity and index value among Iranian patients with multiple sclerosis and its correlation with demographic data and previous therapies

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Background: Anti-JC virus (JCV) antibody index is the predicting factor of progressive multifocal leukoencephalopathy (PML) for patients with multiple sclerosis (MS) who are treated with natalizumab.

Methods: This cross-sectional study assessed all received anti-JCV antibody test results of Iranian patients with MS between January 2014 and December 2016. Demographic data and disease characteristics were also obtained. After data quality control, statistical analysis was done using logistic regression.

Results: Among 803 patients with MS who were observed, the prevalence of anti-JCV antibody positivity was 67.9% (mean of index = 2.23; standard deviation (SD) = 1.16), and 67.6% of positive patients had index ≥1.5. Males were more anti-JCV antibody positive than females (81.7% and 64%, respectively; sig. <0.001, crude odds ratio (OR) = 2.51, confidence interval (CI): 1.65–3.81). Patients ≤50 years had higher positivity prevalence compared to patients ≤18 years (sig. = 0.021; adjusted OR = 3.45, CI: 1.20–9.86). Patients who lived in cold regions had significantly more prevalence of positivity (no. of cases = 403; sig. = 0.043 and crude OR = 1.86, CI: 1.02–3.39) and higher rate of index ≥1.5 (sig. = 0.017; crude OR = 3.99, CI: 1.79–8.88). Disease onset age between 28 and 37 years was more positive compared to 18–27 years ($N = 480$; sig. = 0.02; adjusted OR = 1.85, CI: 1.09–3.14) but correlated reversely with index (sig. = 0.01).

Conclusion: Age, male gender, onset age, and cold area residency significantly influenced anti-JCV antibody positivity prevalence. Only age of onset and cold area residency related to the index. No significant difference was observed between the previous type of disease-modifying drugs, dosage and duration of treating with them, and anti-JCV antibody positivity and its index.

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Preliminary results of the OPERA I and OPERA II open-label extension study

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Background: The efficacy and safety of ocrelizumab in relapsing multiple sclerosis (RMS) have been demonstrated in the OPERA trials. Upon completion of the controlled treatment period, all patients were eligible to enter an ocrelizumab open-label extension (OLE) phase. The objective is to preliminarily assess annualized relapse rate (ARR) at 144 weeks among patients with RMS who received ocrelizumab or interferon beta-1a (IFNβ-1a) in the Phase III 96-week OPERA I and II trials, followed by ocrelizumab in an OLE.
Methods: During the controlled treatment period, patients received intravenous ocrelizumab 600 mg every 24 weeks or subcutaneous IFNβ-1a 44 μg three times weekly for 96 weeks. During the OLE, patients from the IFNβ-1a group were switched to ocrelizumab.
Results: Patients from OPERA I (ocrelizumab, 352/410; IFNβ-1a, 326/411) and OPERA II (ocrelizumab, 350/417; IFNβ-1a, 297/418) enrolled in the OLE. At the time of analysis, 317 (90.1%) and 322 (92.0%) continuous ocrelizumab patients and 307 (94.2%) and 268 (90.2%) patients switching from IFNβ-1a in OPERA I and II, respectively, had ≥48 weeks of follow-up in the OLE (144 weeks total). Across groups, patients received a median of two doses of ocrelizumab in the OLE. Among patients switching from IFNβ-1a to ocrelizumab, the unadjusted ARR improved from 0.245 and 0.254 over 96 weeks in OPERA I and II, respectively, to 0.092 and 0.115 in the OLE. Among continuous ocrelizumab patients, the unadjusted ARR was 0.136 and 0.138 in OPERA I and II, respectively; during the OLE, the ARR in this group was 0.118 and 0.100, respectively. Imaging metrics will be presented.
Conclusion: Patients who originally received ocrelizumab in the OPERA studies continued to have favorable ARR outcomes in the OLE. Patients who switched from IFNβ-1a to ocrelizumab in the OLE rapidly experienced ARR outcomes consistent with those of patients who received continuous ocrelizumab.

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The prevalence of thyroid functional disorders and autoimmune diseases in MS patients treated with interferon beta

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Background: The incidence of thyroid dysfunction and autoimmune diseases in multiple sclerosis (MS) patients who received interferon has been reported in various studies . The mechanism by which interferon therapy leads to thyroid disease is unknown but the results of various studies suggest interactions of the immune system with the direct toxic effects of interferon on thyroid cells. However, there is not much information about these damages in MS patients who take interferon for a long time. Due to this limitation, this study was conducted with the aim of determining the prevalence of thyroid functional disorders and autoimmune diseases in patients with MS treated with interferon beta for less than 5 years.
Methods: One hundred MS patients who had been treated with interferon beta (the case group) and 30 MS patients who had not yet started treatment with interferon (the control group) were included in the study. All patients were examined for the presence of thyroid disorders (using the following tests: TSH, free-T3, and free-T4) and for the presence of autoimmune thyroid disease (using the following tests: anti-TPO and anti-TG).
Results: The prevalence of functional disorders (18% vs. 3.3% and $p = 0.04$) and the prevalence of autoimmune thyroid diseases (38% vs. 7.16% and $p = 0.02$) was significantly higher in patients with MS taking interferon beta than MS patients not taking interferon beta. Also, there was a significant relationship between the duration of consumption of interferon beta with thyroid dysfunction (p =0.03) and with autoimmune thyroid disease (p =042).
Conclusion: The findings of our study showed that in MS patients there is a significant relationship between the prevalence of functional disorders and the prevalence of autoimmune thyroid diseases with consumption and duration of consumption of interferon beta. These findings indicate the need for careful and systematic investigation of MS patients after treatment with interferon in order to detect any thyroid damages early and ensure appropriate treatment measures are taken in the early stages.

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Demographic and clinical feature among patients with neuromyelitis optica in Iran

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Background: Neuromyelitis optica (NMO) is a rare disease and epidemiological data on NMO are limited. The goal of this study was evaluation of demographic and clinical features of NMO in Caucasian population in Tehran, Iran.
Methods: A cross-sectional study among patients registered with NMO diagnosis was performed in Tehran during 2015–2016. We design a questionnaire to cover the epidemiological and clinical data of NMO in Tehran. Structured face-to-face interviews were conducted with 147 patients. The logistic regression was applied in analysis via software package SPSS.
Results: Among 147 patients, mean age was 36.09 years and 127 (86.4%) were female. Mean of disease onset age was 31.53 years. Totally, 61 (46.6%) patients had a history of head trauma with 59% NMO-Ig G positivity, but it was not significantly higher than patients with no history of head trauma ($p = 0.38$; odds ratio (OR) = 1.44 (0.72–2.87). NMO-IgG was positive in 71 (54.2%) patients and did not differ significantly between male and female (female positivity = 56.3%, male positivity = 42.1%; $p = 0.32$). A total of 42.2% of patients had primary presentation by transverse myelitis (TM) and optic neuritis (ON). In the next rank were patients presented only with TM (25.9%) or ON (18.4%).
Conclusion: NMO is higher among female and younger age. Most NMO patients present with TM and ON. Sex and history of head trauma did not significantly influence NMO-IgG positivity.

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Evaluation of no evidence of progression or active disease (NEPAD) in patients with primary progressive multiple sclerosis in the ORATORIO trial

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Background: Primary progressive multiple sclerosis (PPMS) is characterised by steadily increasing neurologic disability. No evidence of progression or active disease (NEPAD), a novel endpoint that assesses the combined absence of composite disability progression and clinical and magnetic resonance imaging (MRI) disease activity, is investigated here in patients with PPMS.

Methods: In a post hoc exploratory analysis of the ORATORIO trial, 234 placebo- and 465 ocrelizumab-treated patients were evaluated to assess the proportion of patients with NEPAD from baseline to Week 120, defined as having no evidence of progression (NEP; no 12-week confirmed progression of ≥1/≥0.5 points on the Expanded Disability Status Scale if the baseline score was ≤5.5/>5.5 points, respectively; no 12-week confirmed progression of ≥20% on the timed 25-foot walk test and nine-hole peg test), no brain MRI activity (no new/enlarging T2 lesions and no T1 Gd+ lesions) and no protocol-defined relapse. Brain MRI assessments were conducted at baseline and Weeks 24, 48 and 120.

Results: Compared with placebo, ocrelizumab increased the proportion of patients with NEPAD at Week 120 (9.4% vs 29.9%; risk ratio ocrelizumab vs placebo (95% confidence interval (CI)): 3.15 (2.07–4.79); $p < 0.0001$). A consistent effect of ocrelizumab was also observed on all three components of NEPAD. Sensitivity analyses will also be presented.

Conclusion: In ORATORIO, the proportion of patients with NEPAD increased approximately threefold with ocrelizumab compared with placebo. NEPAD may represent a useful composite outcome to assess the absence of clinical and MRI features of disease progression and activity in patients with PPMS.

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Comparing multiple sclerosis disability-adjusted life-years and years lived with disability among Iran and Middle East and North Africa in 2015

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Background: The years lived with disability (YLD) and disability-adjusted life-years (DALYs) are critical health index for quantifying burden of disease.

Methods: Based on epi-visualization interactive tool, we could explore data inputs and epidemiological estimates from the GBD 2015 project to assess multiple sclerosis (MS) in Middle East and North Africa (MENA). MS prevalence and age-adjusted MS YLD and DALY's rates in 2015 for both sexes in MENA were observed by organizing into hierarchy levels 3.

Results: Among 21 countries that were enrolled in this observational study, Iran had the highest age-adjusted DALY rate in both sexes (female: 30.98/100,000 (23.93–39.56) years, male: 21.86/100,000 (17.01–28.42) years) and the lowest was for Kuwait (female: 7.76/100,000 (5.79–10.5) years, male: 6.07/100,000 (14.82–7.52) years); also, the highest age-adjusted YLD rate in both sexes belonged to Iran (female: 18.62/100,000 (13.03–24.55) years, male: 8.78/100,000 (5.95–11.94) years) and the lowest was observed in Kuwait (female: 5.06/100,000 (3.42–6.96) years, male: 3.07/100,000 (2.12–4.15) years). These countries had highest and lowest prevalence of MS in both sexes among MENA countries (Iran female MS prevalence: 57.11/100,000, Kuwait female MS prevalence: 14.72/100,000), (Iran male MS prevalence: 26.5/100,000, Kuwait male MS prevalence: 8.62/100,000). Mean of female DALY in the region was 13.97; standard deviation (SD) = 5.37 years. Mean of male DALY in the region was 10.37; SD = 4.36 years. Mean of female YLD in the region was 8.56; SD = 2.79 years, and for male YLD was 5.29; SD = 1.34 years.

Conclusion: In MENA, Iran had the highest age-adjusted DALY and YLD rate in both sexes which can be related to its highest MS prevalence in the region.

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Years lived with disability changes in five income-level countries during 2000–2015

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Background: The years lived with disability (YLD) is a critical health index for quantifying burden of disease that can be effected by prevalence of multiple sclerosis (MS) and life expectancy (LE) index.

Methods: Based on epi-visualization interactive tool, we could explore data inputs and epidemiological estimates from the GBD 2015 project to assess MS. We compared A-st YLD changes during 2000–2015 according to MS prevalence and LE among five income-level countries by organizing into hierarchy levels 3.

Results: Among five income regions, highest A-st YLD rate in 2000 and 2015 was for high-income countries (2000: 23.65 and 2015: 25.86; 9.36% change rate (CR)); also, they had the highest MS prevalence (2000: 71.92/100,000 and 2015: 78.72/100,000). Low-income countries had the lowest MS prevalence (2000: 6.59/100,000 and 2015: 7.14/100,000) and A-st YLD rate (2000: 2.31 and 2015: 2.5; 8.1% CR), and the same trend was seen between MS prevalence and A-st YLD rate in high- to middle-income region and the opposite in low–middle and middle-income countries. A-st YLD rate decreased in middle- to high-income countries (–6.06% CR; 2000: 5.87, 2015: 5.52) and increased in others with the highest change in low- to middle-income countries (9.57% CR; 2000: 4.08, 2015: 4.47). A-st YLD rate changes in middle-income countries was 6.76% (2000: 3.54, 2015: 3.78) and in Iran as a country with middle to high income was –8.72%

(2000: 14.95, 2015: 13.65). LE percent changes reversely related to income of the countries (low-income LE% change = 16.28% to 4.61% in high-income countries). It decreased A-st YLD rate in all regions by nearly the same trend of A-st YLD percent changes, and again middle- to high-income countries had the most decrease in A-st YLD (11.91% CR).

Conclusion: Increase in LE CR had decreasing effect on A-st YLD changes in the nearly same order in all regions. YLD rate changes were related to MS prevalence changes' trend in all regions except low–middle and middle income in which after adjusting YLD rate by prevalence, the differences of A-st YLD rate changes between middle-, high–middle and high-income countries decreased. The effect of MS prevalence on A-st YLD changes rate was more than life expectancy among different income regions.

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Durable improvements in clinical outcomes with alemtuzumab in patients with active relapsing–remitting multiple sclerosis in the absence of continuous treatment: 7-year follow-up of CARE-MS I patients (TOPAZ study)

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Background: Patients completing at least 48 months of the CARE-MS extension could enrol in the 5-year TOPAZ study (NCT02255656) for further long-term evaluation. Here, we report the 7-year efficacy and safety results from patients in the CARE-MS I study who received alemtuzumab.

Methods: In TOPAZ, patients can receive alemtuzumab retreatment ≥12 months after the previous course or other disease-modifying therapy (DMT) at any time point (both per investigator discretion; no criteria); magnetic resonance imaging (MRI) scans are performed annually. Assessments: annualised relapse rate (ARR); 6-month confirmed disability worsening (CDW); 6-month confirmed disability improvement (CDI); no evidence of disease activity (NEDA); and adverse events (AEs).

Results: Of the 349 CARE-MS I patients who entered the extension, 321 (92%) remained on study until the end of Year 6 and then entered TOPAZ. Of those, 299 (93%) patients remained on study through Year 7. ARR remained low (0.13 at Year 7), and the proportion of patients with either stable or improved EDSS versus baseline remained high (78% at Year 7). Through 7 years, 74% of patients were free from 6-month CDW and 37% achieved 6-month CDI. The majority of patients achieved NEDA in each year (Year 3: 62%; Year 4: 60%; Year 5: 62%; Year 6: 58%; and Year 7: 61%). These effects were achieved with 59% of patients receiving no additional treatment (alemtuzumab or other DMT) after their initial two courses of alemtuzumab. Incidences of overall AEs, infusion-associated reactions, and infections decreased over time and were reduced versus the 2-year core study. Thyroid AE incidence peaked at Year 3 and then declined.

Conclusion: Clinical efficacy of alemtuzumab was maintained for 7 years in treatment-naive patients, despite 59% receiving no additional treatment since the initial two courses of alemtuzumab. Additionally, improvement in disability was observed in 37% of the patients. The safety profile of alemtuzumab remained consistent, and the overall incidence of AEs decreased over time. These findings suggest that alemtuzumab may provide a unique treatment approach for patients with relapsing–remitting multiple sclerosis (RRMS), offering durable efficacy in the absence of continuous treatment.

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Assessment of clinical disease activity and disability improvement by number-needed-to-treat analyses in patients with relapsing multiple sclerosis treated with alemtuzumab or ocrelizumab

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Background: We determined the number-needed-to-treat (NNT) to prevent clinical disease events and achieve disability improvement versus subcutaneous (SC) interferon beta (IFNβ)-1a in relapsing multiple sclerosis (MS) studies of alemtuzumab and ocrelizumab.

Methods: NNT values were derived from post hoc analyses of the 2-year data from the alemtuzumab 12 mg and ocrelizumab 600 mg studies. This analysis used alemtuzumab data from patients with active relapsing–remitting MS (RRMS; ≥2 relapses within the last 2 years, with one or more relapse in the previous year) who were treatment-naive (CAMMS223 (NCT00050778) and CARE-MS I (NCT00530348), N = 786) and those who had an inadequate response (≥1 relapse) to prior therapy (CARE-MS II (NCT00548405), N = 628). Ocrelizumab data were analysed from the OPERA I (NCT01247324, N = 821) and II studies (NCT01412333, N = 835) in patients with two or more clinical relapses within the previous 2 years or one clinical relapse in the previous year.

Results: Baseline mean Expanded Disability Status Scale (EDSS) scores (CAMMS223/CARE-MS I: 2.0; CARE-MS II: 2.7; OPERA I: 2.9; OPERA II: 2.8), mean MS duration (CAMMS223/CARE-MS I: 1.9 years; CARE-MS II: 4.5 years; OPERA I and II: 6.7 years in each study) and mean number of relapses in the previous 2 years (CAMMS223/CARE-MS I: 2.5;

CARE-MS II: 2.8; OPERA I/II: 1.8 in each study) varied across the trials. Both alemtuzumab and ocrelizumab significantly reduced annualized relapse rate (ARR) and confirmed disability worsening (CDW) versus SC IFNβ-1a. NNT values versus SC IFNβ-1a were lower with alemtuzumab than ocrelizumab to prevent one relapse (CAMMS223/CARE-MS I: 5; CARE-MS II: 4; OPERA I/II: eight each), CDW in one patient (CAMMS223/CARE-MS I: 15; CARE-MS II: 13; OPERA I: 23; OPERA II: 21) and clinical disease activity (CDA) in one patient (CAMMS223/CARE-MS I: 5; CARE-MS II: 6; OPERA I/II: 8 each). NNT values versus SC IFNβ-1a to achieve CDI in one patient were also lower with alemtuzumab than ocrelizumab (pooled CAMMS223/CARE-MS I/CARE-MS II: 10; pooled OPERA I/II: 25).

Conclusion: Acknowledging population differences in the datasets, fewer patients required treatment with alemtuzumab than ocrelizumab to prevent clinical events and achieve CDI over 2 years in SC IFNβ-1a comparator studies. Further real-world clinical experience will help confirm these findings.

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Assessment of availability and usefulness of multiple sclerosis health education resources in Arabic

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Background: Multiple sclerosis (MS)-related health education and reliable information is significant to patients with MS (especially the newly diagnosed). Mounting evidence suggests that credible and continuous health information for patients improves symptoms' management and treatment compliance and thereby contributes to better health outcomes. Despite the existence of many credible and evidence-based information resources in many languages, such information sources are lacking for Arabic-speaking patients and families, and little is known about the perceived trust in such information sources.

Methods: The cross-sectional study incorporated two phases. Phase 1 was a pilot study that included developing and validating the questionnaires to be used in the main study. It was conducted in a sub-sample of patients with MS, family/friends ($n = 15$), and a group of healthcare professionals ($n = 5$) for content validity and clarity of the two developed questionnaires. Phase 2 was conducted on main study population of selected MS-related population (patients and family/friends; $n = 217$. The questionnaires covered items on demographics; disease-related questions; information resources used by respondents; and knowledge about, level of trust, and satisfaction on the newly enhanced Arabic website (evidence-based) developed by the Saudi MS Advisory Group.

Results: The distribution of the patients with MS sample is similar to that of the general MS population in Saudi where female-to-male ratio is 2:1, 65% of respondents were university graduates or above, and 50% were employed. In addition, 65% of the patients suffered previous relapses in the past 5 years with 52% having partial recovery and 41% with complete recovery. A total of 68% of all respondents had little or no prior knowledge about the disease until diagnosis. They also showed that the Internet and social media outlets were the sources most used by respondents in seeking MS-related health information regardless of their characteristics (~90%). Availability of information through Internet and social media outlets was found to be significantly higher than other traditional media and news outlets (p-value = 0.01, odds ratio (OR): 3.65).

Conclusion: Although physicians are still regarded as the most trusted source of health information for patients with MS, the Internet and social media are the widely used sources of information for most of them. This has important implications for the delivery and dissemination of MS-related health information for Arabic-speaking patients and their communities.

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Relationship between neutrophil-to-lymphocyte ratio and stress in patients with multiple sclerosis

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Background: Multiple sclerosis (MS), a disease of autoimmunity and inflammation, is characterized by deterioration of the myelin sheath that protects the nerve fibers. The high levels of neutrophils in serum may be related to the chronic inflammation and caused by other triggers such as infections that have been associated with relapses in MS.

Methods: It was a retrospective study on 60 patients with MS and 60 age- and sex-matched healthy controls. Patients with MS were evaluated for their eligibility for inclusion as complete clinical data containing laboratory records, complete blood count (CBC), and disease activity score (DAS) score. Matched healthy subjects without any risk factors or chronic diseases were included as controls. We measured DAS score, neutrophil-to-lymphocyte ratio (NLR), calcium, phosphate, magnesium, chloride, alkaline phosphatase, and albumin serum levels in patients with MS and in healthy controls.

Results: The mean age was not significantly different in both case and control groups. The case and control groups were similar in terms of sex; however, the majority of the MS group was female. The NLR values of patients with MS were significantly higher than those of the healthy controls ($p < 0.001$). The NLR values were also significantly ($p < 0.001$) correlated with stress score.

Conclusion: MS is a disease of axonal degeneration and demyelination leading to unalterable damage to the central nervous system (CNS). The transfer of autoreactive T cells from the blood to the CNS is the key moment in the pathogenesis of MS, which starts a whole flow of imbalances in various chronic inflammatory diseases. NLR could be considered as a quick, cheap, easily measurable, and inflammatory marker for assessment of inflammation in patients with MS. The role of NLR in MS must be explored further.

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An update on pregnancy outcomes following ocrelizumab treatment in patients with multiple sclerosis and other autoimmune diseases

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Background: Ocrelizumab, a humanised monoclonal antibody that selectively targets CD20+ B cells, is approved by the Food and Drug Administration for the treatment of relapsing and primary progressive forms of multiple sclerosis (MS) and has also been studied in clinical trials for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The objective is to provide an update of pregnancy outcomes in women treated with ocrelizumab during clinical trials.

Methods: This analysis includes pregnancies in women with MS, RA and SLE in ocrelizumab clinical trials (dose range 20–2000 mg) up to 31 January 2017. Across trials, women of childbearing potential were required to use two methods of contraception and continue contraception for 48 weeks after the last ocrelizumab infusion or until B cells repleted, whichever was longer. Urine pregnancy tests were performed at all infusion visits; if positive, dosing was stopped and the result confirmed with a serum pregnancy test. An embryo/foetus was considered exposed to ocrelizumab in utero if the last infusion occurred within 3 months of conception or during pregnancy or if the date was unknown. All pregnancies occurring during clinical trials were followed to determine outcome.

Results: As previously reported, between 2008 and 14 September 2015, 46 women randomised to ocrelizumab in clinical trials (15 MS, 10 SLE, 21 RA) reported 48 pregnancies (15 MS, 11 SLE, 22 RA). This cumulative update provides approximately 16 months' additional data on pregnancies in clinical trials up to 31 January 2017 and will review 58 pregnancies reported in 56 women (25 MS and 31 non-MS). Among the 25 pregnancies in patients with MS, 13 were considered to have foetal ocrelizumab exposure. A total of 11 pregnancies had no foetal ocrelizumab exposure and one pregnancy is not assessable for foetal ocrelizumab exposure.

Conclusion: As a large proportion of patients with MS are women of reproductive age, pregnancy outcomes in patients exposed to ocrelizumab are important to understand. B-cell levels in neonates following maternal exposure to ocrelizumab have not been studied in clinical trials and the effect of ocrelizumab on the immune system of the newborn is unknown. Transient peripheral B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to other anti-CD20+ antibodies during pregnancy.

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Safety of ocrelizumab in multiple sclerosis: Updated analysis in patients with relapsing and primary progressive multiple sclerosis

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Background: Two identical Phase III trials in relapsing multiple sclerosis (RMS; OPERA I (NCT01247324) and OPERA II (NCT01412333)) and the Phase III trial in primary progressive MS (PPMS; ORATORIO (NCT01194570)) evaluated the safety and efficacy of ocrelizumab. Ongoing safety reporting on disease-modifying therapies for MS is crucial to understanding the long-term benefit–risk profile. The objective is to report safety data from the follow-up of the global clinical trials of ocrelizumab in RMS and PPMS.

Methods: In the OPERA studies, patients with RMS were randomised in a 1:1 ratio to receive intravenous ocrelizumab 600 mg every 24 weeks or subcutaneous interferon beta-1a (IFNβ-1a) 44 µg three times weekly for 96 weeks. In the ORATORIO trial, patients with PPMS were randomised in a 2:1 ratio to receive intravenous ocrelizumab 600 mg or placebo every 24 weeks for at least 120 weeks. Following completion of the controlled treatment periods, Phase III patients were eligible to enter the ocrelizumab open-label extension (OLE) phase of the trial. In a Phase II study in relapsing–remitting MS, patients were randomised in a 1:1:1:1 ratio to receive ocrelizumab 600 mg, ocrelizumab 2000 mg, placebo or intramuscular IFNβ-1a through Week 24, followed by ocrelizumab every 24 weeks through Week 96. Following a treatment-free period, eligible patients from the Phase II trial entered a long-term OLE in which ocrelizumab 600 mg was administered every 24 weeks. Safety outcomes were reported for all patients administered with ocrelizumab in Phase II and III MS clinical trials, including patients who switched to ocrelizumab from comparators. Long-term safety data will continue to be reported, particularly for serious infections, malignancies and any new signals that could arise.

Results: As of 17 February 2017, 2301 patients with MS received ocrelizumab, resulting in 7748 patient-years (PY) of exposure. Reported rates per 100 PY (95% confidence interval) were as follows: adverse events (AEs), 226 (222–229); serious AEs, 7.18 (6.59–7.80); infections, 71.3 (69.5–73.2) and serious infections, 1.86 (1.57–2.19). The incidence rate of malignancy was 0.454 (0.316–0.632).

Conclusion: The updated safety profile in the ocrelizumab MS all-exposure population is generally consistent with that seen during the controlled treatment period in the RMS and PPMS populations. Additional data from the ongoing follow-up will be reported.

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Rapidity of onset of ocrelizumab clinical efficacy in relapsing multiple sclerosis

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Background: In relapsing multiple sclerosis (RMS), rapid control of clinical disease activity is an important treatment goal to minimize subsequent disability worsening. Ocrelizumab, a humanized monoclonal antibody that selectively targets CD20+ B cells, was superior in reducing clinical and magnetic resonance imaging (MRI) measures of disease activity compared with interferon beta-1a (IFNβ-1a) over 96 weeks in two identical phase III trials in RMS (OPERA I and OPERA II). The objective is to assess the dynamics of onset of ocrelizumab effect on the risk of relapse over time and relapse rate by epoch compared with IFNβ-1a in the pooled OPERA I and OPERA II studies in RMS.
Methods: In the OPERA studies, patients were randomized 1:1 to receive intravenous ocrelizumab 600 mg every 24 weeks or subcutaneous IFNβ-1a 44 μg three times weekly for 96 weeks. The primary endpoint in the individual studies was annualized protocol-defined relapse rate (ARR) by Week 96. The risk of first onset of protocol-defined relapse at various time points and ARR through Week 96 and at 8-, 24-, and 48-week epochs in the pooled OPERA studies were evaluated in post hoc exploratory analyses.
Results: In the pooled analysis, ocrelizumab reduced ARR from baseline to Week 96 by 46.5% versus IFNβ-1a (0.156 vs 0.291; $p < 0.0001$). Kaplan–Meier analysis showed that ocrelizumab reduced the cumulative probability of relapse versus IFNβ-1a as early as Week 8 (hazard ratio: 0.02 vs 0.04, $p = 0.0142$). Reductions in ARR with ocrelizumab versus IFNβ-1a were also observed in the baseline–Week 8 (0.12 vs 0.27; $p = 0.0045$), baseline–Week 24 (0.18 vs 0.30; $p = 0.0009$), and baseline–Week 48 (0.16 vs 0.30; $p < 0.0001$) epochs.
Conclusion: In a pooled analysis of the OPERA studies, ocrelizumab reduced relapse occurrence versus IFNβ-1a throughout 96 weeks, with significant reductions observed by Week 8.

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Long-term effect of delaying disease-modifying therapy in patients with multiple sclerosis due to pregnancy planning

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Background: The effect of pregnancy on long-term disability in women with relapsing–remitting multiple sclerosis (MS) is poorly understood. Our aim is to determine the association between delaying disease-modifying therapy (DMT) for pregnancy planning and long-term disability, as measured by the Expanded Disability Status Scale (EDSS), in women with relapsing–remitting MS.
Methods: Using data from the Calgary MS Clinic database, we identified 426 women with EDSS <5, who delayed starting DMT for more than 1 year after it was recommended during the period 1999–2006. Thirty-seven consenting women declined DMT due to planned pregnancy. EDSS at diagnosis was compared with EDSS at 5, 7, 10, and 15 years. The association between the cumulative time on DMT during the first 5 years of MS and EDSS change at 5, 7, 10, and 15 years was determined. EDSS change in these women was then compared with EDSS change in two control groups of women also with relapsing–remitting MS, diagnosed between age 18 and 40 years, and who had an EDSS <5 when first advised to start DMT between 1999 and 2006: 101 women who delayed DMT for reasons other than pregnancy planning and 173 women who started DMT within 1 year of diagnosis.
Results: Mean follow-up of the 37 women who delayed DMT due to planned pregnancy was 14.05 years. Prior to the diagnosis of MS, 86.5% were nulliparous compared with 18.9% at the end of follow-up. Mean time to pregnancy was 2.38 years from MS diagnosis and 0.84 years from declining DMT for pregnancy planning. Eventually, 67.6% of the patients started DMT. Mean time to initiating DMT was 4.02 years after declining DMT for pregnancy planning. Confirmed relapses occurred in 70.3% of women between declining DMT for pregnancy planning and starting DMT; the mean time to a relapse was 1.92 years. There was an increase in the mean EDSS score 15 years after diagnosis of 1.13 points (paired *t*-test, $p = 0.002$) among women who declined DMT for pregnancy planning. There was a moderate to high moderate negative correlation between the cumulative time on DMT during the first 5 years after the diagnosis of MS and EDSS change at 7 years ($R = –0.49$, $p = 0.008$), 10 years ($R = –0.44$, $p = 0.017$), and 15 years ($R = –0.67$, $p = 0.006$). When compared to the two control groups, change in EDSS scores at 5, 7, 10, and 15 years was not significantly different even after adjustment for age and EDSS at diagnosis.
Conclusion: Delaying DMT initiation for a planned pregnancy did not have a major impact of disability over 15 years in our patients despite the frequent occurrence of relapses and statistically significant change in EDSS. Greater time on DMT during the first 5 years after their MS diagnosis was associated with a statistically significant reduction in EDSS change.

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Rapid onset of ocrelizumab suppression of brain MRI activity in relapsing–remitting multiple sclerosis

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Background: To assess the dynamic of onset of ocrelizumab treatment effect on brain magnetic resonance imaging (MRI) activity compared with placebo and interferon beta-1a (IFNβ-1a) in a Phase II study in relapsing–remitting multiple sclerosis (RRMS). Rapid control of subclinical disease activity is an important goal to minimize disability progression in MS. In clinical trials in relapsing MS, ocrelizumab demonstrated superiority in reducing MS disease activity versus placebo and IFNβ-1a.
Methods: In the first 24 weeks of this Phase II trial, patients received placebo ($n = 54$), ocrelizumab 600 mg ($n = 55$), ocrelizumab 2000 mg ($n = 55$), or intramuscular IFNβ-1a 30 μg ($n = 54$). The primary endpoint was the total number of T1 gadolinium-enhancing (Gd+) lesions at Weeks 12, 16, 20, and 24. Further exploratory analyses evaluated the total number of new T1 Gd+ lesions, new T2 lesions, and newly enlarging T2 lesions

by 4-week epochs for ocrelizumab 600 mg versus placebo and IFNβ-1a.
Results: Ocrelizumab reduced the total number of new T1 Gd+ lesions at Week 4 by 62% versus placebo ($p = 0.0423$) and the number of new T1 Gd+ lesions appearing between Weeks 4 and 8 by 97% versus IFNβ-1a ($p < 0.0001$). The mean total number (adjusted rate) of new T2 lesions appearing between Weeks 4 and 8 was 0 for ocrelizumab versus 0.717 for placebo and 0.609 for IFNβ-1a. Ocrelizumab reduced the total number of newly enlarging T2 lesions appearing between Weeks 4 and 8 by 93% versus placebo ($p = 0.0030$) and 90% versus IFNβ-1a ($p = 0.0162$). For each of the above endpoints, between-group differences favoring ocrelizumab versus placebo and versus IFNβ-1a were maintained at subsequent 4-week epochs through Week 24.
Conclusion: In this Phase II trial in RRMS, ocrelizumab demonstrated beneficial effects on brain MRI activity versus placebo and IFNβ-1a as early as Week 4, supporting a rapid onset of action in suppressing brain lesions.

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Association between fatigue and cognition of multiple sclerosis in Hong Kong

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Background: Multiple sclerosis (MS) is one of the common neurological diseases characterized by chronic inflammatory demyelination in central nervous system. Cognitive impairment and fatigue are frequently reported in patients with demyelinating diseases. This cross-sectional study aims to examine the cognitive profile and the correlation of fatigue level and cognitive function and to explore the predictors on the global cognition of patients with MS in Hong Kong.
Methods: In all, 30 participants diagnosed with demyelinating diseases were recruited. A collection of comprehensive cognitive test indices, Modified Fatigue Impact Scale (MFIS), and Kurtzke Expanded Disability Status Scale (EDSS) were used to evaluate the pattern of cognitive impairment, level of fatigue, and physical disability respectively. The performance of each cognitive measure was compared with the normative data in Hong Kong.
Results: Results indicated that 20% of the participants impaired in Hong Kong (HK)-Montreal Cognitive Assessment (MoCA) and there were 26.7% of them identified as fatigue in MFIS (scores ≥38). No statistical significant difference was found in cognitive tests between fatigue and non-fatigue MS. Only trail making test (TMT) part B was moderately correlated with MFIS ($r = –0.406$, $p < 0.05$). Linear regression analysis revealed that EDSS was a significant predictor to HK-MoCA score ($\beta = –1.192$, $p < 0.01$).
Conclusion: The study outlined the cognitive profile of MS cohort in Hong Kong and drew the conclusion that fatigue is correlated with the mental processing speed but not the global cognition, and neurological disability is a moderate predictor to the cognitive performance in patients with MS.

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The prevalence and incidence of MS and familial MS in Tehran Province, Iran

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Background: In recent years, the prevalence of multiple sclerosis (MS) has increased significantly in Tehran. Positive familial history of MS is one of the known factors increasing the risk of MS presentation. In this study, we estimated the prevalence and incidence of MS in Tehran in the year 2016 while assessing associations among most important baseline characteristics of the patients.
Methods: A cross-sectional study was conducted in Iranian MS Society data from 1999 to 2016 and it investigated the most important variables related to the individual level for familial MS (gender, age at disease onset, and familial history of MS). Multiple regression was used to indicate the predictors of onset age of MS via SPSS.
Results: In all 18,061 patients with MS were included. The crude prevalence was 136/100,000 (95% confidence interval (CI): 114–160), with female-to-male ratio of 3.06:1. MS age-standardized incidence rate was 1.8/100,000 of population (95% CI: 1.3–7.2). About 6.89% of the population had early-onset MS (≤18 years old); 13.37% of the male patients and 12.24% of the female patients had a history of familial MS. A total of 14.86% of the individuals with early-onset MS had familial history of MS comparing to 12.35% of the individuals with onset age more than 18 years old, $p = 0.01$. The mean onset age of MS was 28.50, in individuals without familial history of MS (95% CI: 28.42–28.70; $p = 0.007$), 29.15 in males (28.88–29.42) and 28.29 in females (28.14–28.43). Gender was a strong significant predictor for onset age ($p < 0.001$).
Conclusion: While having increased MS prevalence in Tehran, the female to male ratio and incidence rate (comparing to previous studies) have decreased. The mean onset age of MS was significantly higher in individuals without familial history than individuals with history of familial MS. Therefore, further research on genetic epidemiology of MS is needed.

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The prevalence and characteristics of neuromyelitis optica spectrum disorder in Tehran, Iran

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Background: Neuromyelitis optica (NMO) is an infrequent demyelinating disease, and epidemiological information on NMO is rare. The aim of this study was to estimate the prevalence, clinical features, and serology of NMO in Caucasian population in Tehran, Iran.
Methods: A cross-sectional study was performed during 2015–2016 in Tehran among patients registered with NMO diagnosis. A structured questionnaire was designed in MS Research Center to

measure the baseline characteristic, severity of symptoms, and significant epidemiological variables which were associated with NMO. The study was described for 103 registered patients, and data were collected from hospital database registry system and patient's information through face-to-face interview. The logistic regression was applied in analysis by software package SPSS.
Results: The prevalence of NMO in Tehran was 0.86/100,000 in 2016 with point prevalence rate of 1.35 and 0.26/100,000, respectively, for females and males. Female-to-male ratio was 5:1. The mean age at the disease onset was 31.54 years old. NMO-IgG was positive in 44 (46.8%), and first presenting symptoms among patients were transverse myelitis (TM) in 29 (28.2%), optic neuritis (ON; 23.3%), unilateral declined visual acuity (17.47%), TM + ON (46.6%), and NMO with other appearances in 2 (1.9%). Based on our study, ON had significant association with female gender. The adjusted odds ratio for sex was estimated for depression (odds ratio (OR) = 6.83; 95% confidence interval (CI): 1.47–31.71), migraine (OR = 1.27; 95% CI: 1.13–1.42), and hypothyroidism (OR = 1.25; 95% CI: 1.12–1.39).
Conclusion: We indicated that the risk of NMO is significantly higher among females and younger age group. Based on the results obtained from our study, ON had significant association with female gender and patients who had background of depression, migraine, and hypothyroidism.

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Environmental risk factors in neuro myelitis optica

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Background: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disorder of the central nervous system. The aim of this study was to discover the environmental risk factors associated with a large sample of people with NMO.
Methods: A case–control study was conducted in Tehran among 100 patients with a definite diagnosis of NMO. A structured questionnaire was designed to measure important epidemiological variables. A total of 400 control population were selected randomly from 15- to 50-year-old residents of Tehran through digit dialing (RDD). Logistic regression was used to estimate unadjusted, adjusted odds ratios (ORs), and 95% confidence intervals (CIs) via software package SPSS, version 23.
Results: Compared with the control population, in NMO patients the adjusted OR for low dairy consumption per week was OR = 18.09 (95% CI: 6.91–47.37), followed by low sea food intake (OR = 13.91; 95% CI: 6.13–31.57), low number of egg consumption (OR = 9.39; 95% CI: 4.03–21.86), low red meat consumption (OR = 3.07; 95% CI: 1.68–5.62), low chicken consumption (OR = 4.05; 95% CI: 1.59–10.35), and low fruit and vegetable consumption (OR = 6.23; 95% CI: 3.07–12.62). The lower light physical activity (OR = 6.32, 95% CI: 3.08–12.95) and lower heavy physical activity (OR = 16.11, 95% CI: 7.03–36.91) among patients had increased risk of NMO. A history of head trauma was risk of NMO (OR = 8.39, 95% CI: 4.97–14.16). A family aggregation of type 1 diabetics in sibling and mother was observed (OR = 12.63) and (OR: 7.61), respectively.
Conclusion: The low consumption of dairy, sea food, red meat, egg, fruit/vegetables, low physical activity and sun exposure, and head trauma were the main environmental risk factors in NMO.

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Effect of vitamin D replacement on cognition in patients with multiple sclerosis

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Background: Multiple sclerosis (MS) is associated with deficient serum 25 hydroxyvitamin D (25 (OH)D) level and cognitive impairment. The aim of this study is to evaluate cognitive performance in patients with MS with deficient 25 (OH)D (<25 ng/mL) compared to patients with sufficient levels (>35 ng/mL) and then to evaluate the change in cognitive performance after 3 months of vitamin D3 oral replacement.
Methods: In all, 88 patients with relapsing–remitting MS and clinically isolated type of MS, older than 18 years, treated with interferon beta were enrolled. Cognitive testing was performed at baseline and at 3 months using the Montreal Cognitive Assessment (MoCA), Stroop, Symbol Digit Modalities (SDMT), and Brief Visuospatial Memory Test (BVMT-R). Serum 25 (OH)D was measured at baseline and at the end of the study.
Results: Vitamin D3 replacement improved the cognitive performance in patients with MS after 3 months on MoCA and BVMT-Delayed Recall (DR). Sufficient serum 25 (OH)D level predicted better cognitive performance on the BVMT-DR at baseline ($\beta = 1.74$, $p < 0.008$) and 3 months ($\beta = 1.93$, $p < 0.01$) after adjusting for all measured confounding variables.
Conclusion: Vitamin D3 replacement could improve cognitive performance in patients with MS and make a significant difference in the patient's quality of life.

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Evaluation of sleep quality and risk assessment of obstructive sleep apnea among patients with MS

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Background: Multiple sclerosis (MS) is a demyelinating disease characterized by deficient neural conduction and axonal loss. Fatigue as a common complaint of patients with MS has several possible explanations. Sleep disorder contributes to chronic fatigue, and decreased sleep quality is reported among patients with MS. We aimed to evaluate the sleep quality and risk of obstructive sleep apnea (OSA) among patients with MS and assess the correlation between the severity of the disease and sleep quality.
Methods: In all, 514 patients with MS including 70 men and 435 women were enrolled in the study. Age range was 13–67 years. Basic demographic and disease characteristic data were collected from all patients. Disease severity was assessed using Extended

Disability Score Scale (EDSS). Sleep quality and sleepiness were assessed by Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Score (ESS). Likelihood of OSA was assessed using the Berlin and STOP-Bang questionnaire.

Results: Regarding the quality of sleep, the mean ± standard deviation (SD) of PSQI score was 6.6 ± 3.2 with 60.9% of the patients having poor sleep quality. ESS results, however, showed that 8.6% of the patients reported mild to severe sleepiness during the day. With regard to likelihood of OSA, evaluation of patients with STOP-BANG questionnaire revealed that 13% of the patients had high risk for OSA; Berlin questionnaire also indicated that 21.2% of the patients had high likelihood of sleep disordered breathing. PSQI scores were weakly correlated to the patients' EDSS score ($p = 0.02$, $r = 0.4$). Berlin questionnaire results were also correlated to the patients' EDSS score ($p = 0.04$, $r = 0.35$).

Conclusion: Our results indicate that patients with MS have poor sleep quality and that OSA could be partially relevant. We also found that MS severity directly affects sleep quality.

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The use of natalizumab in pediatric patients with active relapsing multiple sclerosis: A prospective study

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Background: Pediatric multiple sclerosis (MS) has been increasingly recognized. In the absence of approved disease-modifying therapies (DMTs) for pediatric patients, clinicians resort to data extrapolated from clinical trials conducted in adults with MS. The objective of this article was to study the effectiveness and safety of natalizumab in patients with pediatric MS.

Methods: Patients with pediatric MS (age < 18 years) who had been treated with natalizumab were followed up prospectively as part of the national MS registry. Data of relapsing patients who had at least 1-year follow-up data were analyzed. The primary outcome measure was the annual relapse rate after natalizumab treatment. Secondary outcome measures included the mean change in disease progression measured by the Expanded Disability Status Scale and the proportion of patients with radiologic activity (gadolinium-enhancing or new T2 lesions) at the last follow-up visit.

Results: In all, 32 patients with pediatric MS had been treated with natalizumab for at least 12 months, of whom 72% were females. The mean age at onset and disease duration was 14.9 ± 2.6 and 5.1 ± 3.1 years, respectively. Most patients ($n = 21$, 66%) had breakthrough disease on first-line DMTs. The mean number of natalizumab infusions was 34.5 ± 18. The annual relapse rate was significantly reduced (1.66 ± 0.5 vs 0.06 ± 0.25; $p < 0.001$), whereas the mean Expanded Disability Status Scale improved (3.3 ± 1.3 vs 2.2 ± 1.0; $p < 0.001$) at the last follow-up visits. The proportion of patients with magnetic resonance imaging activity was significantly reduced (93.8% vs 12.5%; $p < 0.001$). No major adverse events were observed.

Conclusion: In our pediatric MS who had cohort with aggressive or breakthrough disease, treatment with natalizumab was effective in reducing clinical and radiologic disease activity. Natalizumab has a similar clinical efficacy and safety profile as in adult MS.

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Effectiveness and safety of dimethyl fumarate treatment in patients with relapsing multiple sclerosis: A real-world evidence

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Background: Dimethyl fumarate (DMF) has been recently approved as a disease-modifying therapy for the treatment of multiple sclerosis (MS). Post-marketing studies are important to confirm what was established in clinical trials.

Methods: Using the national MS registry, we prospectively assessed relapsing patients with MS who had been prescribed DMF for at least 6 months. Primary outcome measure was the proportion of relapse-free patients at last follow-up visit. Secondary outcome measures were the mean change in Expanded Disability Status Scale (EDSS) and the proportion of patients with radiological activity (gadolinium-enhancing or new T2 lesions) at the last follow-up visit. Absolute lymphocyte count (ALC) was assessed at baseline (within 6 months prior to DMF initiation) and at one or more times during DMF treatment 3 months post-initiation.

Results: Of 134 patients identified, 119 were eligible and included in the analysis. Women represented 59.7% of the studied cohort. Mean age and mean disease duration were 33.5 ± 11.1 and 8.3 ± 7 years, respectively. A total of 75.6% of the patients received prior disease-modifying therapies. Mean duration of DMF exposure was 20.5 ± 9.5 months. The proportion of relapse-free patients increased significantly from 51.2% to 89.9% ($p < 0.0001$), while the mean EDSS score decreased from 2.8 ± 1.8 at baseline to 2.3 ± 1.7 ($p = 0.058$) at last follow-up visit. The proportion of patients with magnetic resonance imaging (MRI) activity decreased significantly from 61.1% to 15.1% ($p < 0.0001$). The mean ALCs decreased from 2170 to 1430 cells/μL (34% decrease). Lymphopenia was seen in 13 (10.9%) patients, of whom 3 (2.5%) patients had grade 3 lymphopenia necessitating discontinuation of DMF. Although no serious adverse events were reported, 19.3% of patients discontinued DMF.

Conclusion: In clinical practice, DMF appeared to be effective in reducing disease activity and progression of disability throughout the observational period. DMF was well tolerated with no serious adverse events. ALC profiles in DMF-treated patients were generally stable throughout the observational period. The proportion of patients who developed severe lymphopenia was similar to figures in clinical trials.

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Rate of multiple sclerosis relapse occurrence in pregnancy and post-partum period

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Background: Although multiple sclerosis (MS) relapse rates are often reduced during pregnancy, disease reactivation may be of concern after withdrawals of disease-modifying therapies (DMTs) prior or at the time of pregnancy confirmation.

Methods: We conducted a retrospective cross-sectional study using the national Kuwait MS registry to identify pregnant women between 1 October 2011 and 30 September 2016. Data on demographics and clinical characteristics including relapses, prior use of DMTs, and pregnancy outcome were extracted. The primary outcome measure was the rate of relapse occurrence during pregnancy and the post-partum period. Furthermore, we investigated the relationship between the use of different DMTs and their washout periods and relapse occurrence.
Results: The medical records of 73 pregnancies (68 patients) were reviewed. Mean age and mean disease duration at the time of pregnancy confirmation were 28.2 ± 4.2 and 4.11 ± 3.9 years, respectively. Most patients (88.2%; $n = 60$) were on DMTs in the year prior to pregnancy. Beta-interferons were the most prescribed medications (42.6%) followed by natalizumab (25%) and fingolimod (19.1%). Thirteen relapses occurred in 16.2% of patients during pregnancy, 7 and 5 of which occurred in first and third trimesters, respectively. Natalizumab and fingolimod were associated with relapses in the first trimester. Additional 10 relapses were recorded during post-partum period within 6.2 ± 5.6 weeks of delivery. Four miscarriages/spontaneous abortions were recorded.
Conclusion: The rate of relapse occurrence during pregnancy is higher than expected. Most relapses clustered in the first trimester suggesting that disease reactivation was associated with withdrawal of high-efficacy DMTs and closely related to the washout period prior to pregnancy. Future studies are needed to address the adequate washout period prior to conception and best time to reinstitute DMTs in highly active patients.

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Economic burden of multiple sclerosis on Kuwait healthcare system

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Background: Multiple sclerosis (MS) is a chronic neurological disease with heavy economic and social burdens resulting in significant disability and social dependence. The prevalence of MS is in an upward trend in Kuwait reaching 85.05/100,000 in 2011.
Methods: A cross-sectional study using Kuwait National MS registry was conducted to estimate the costs of utilization of resources. Data of patient demographics, clinical features, and diagnostic/therapeutic utilizations between 2011 and 2015 were extracted. This study aims to measure the cost of health resources' utilization by patients with MS and to examine the difference in utilization and its attributed costs among patients with different types of MS and Expanded Disability Status Scale (EDSS) scores. Kruskal–Wallis test was used to examine the difference between costs in different types of MS and EDSS scores.
Results: By end of 2015, 1344 patients with MS were included in the registry, of which 75.9% were of relapsing–remitting (RR) form and 83.3% had EDSS scores ≤3. The average annual cost per patient with MS has increased from 4532 KD in 2011 to 6753 KD in 2015. Utilization of disease-modifying therapies (DMTs) was the main driver of costs reaching 89.9% in 2015. The number of treated patients increased by 12.7% due to the availability of oral DMTs. Throughout the 5-year period, relapse severity decreased as the proportion of relapses treated in ambulatory settings increased by 5.8% while hospitalizations decreased by 2.6%. There was a significant difference between the average cost per patient in different types of MS and different EDSS categories ($p < 0.0001$), with patients with RR course and moderate EDSS score (3.5–6) having the highest average of 7144 KD and 10,544 KD, respectively.
Conclusion: MS has a significant economic burden on the Kuwait healthcare system. DMTs seem to be the main driver of cost.

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Assessment of lymphopenia in patients with multiple sclerosis treated with dimethyl fumarate in a real clinical setting

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Background: Dimethyl fumarate (DMF), a disease-modifying therapy for multiple sclerosis (MS), causes lymphopenia in a fraction of patients. Since lymphocytes contribute to MS pathology, lymphopenia may be a biomarker for response to the drug or for serious adverse events such as infections.
Methods: Using the national MS registry, a retrospective study was conducted to identify patients with MS who received DMF. Patients included in the analyses received at least 3 months' prescription and had absolute lymphocyte count (ALC) values available at baseline (within 3 months prior to DMF initiation) and at least twice 3 months post DMF initiation. Grades of lymphopenia were assigned according to the common terminology criteria for adverse events: grade 1 ALC <lower limit of normal to 800/mm^3, grade 2 ALC <800–500/mm^3, and grade 3 ALC <500–200/mm^3. The primary outcome of the study is to evaluate ALCs in patients with MS treated with DMF in a real clinical setting.
Results: A total of 54 patients met the inclusion criteria, of whom 66.7% were females. Mean age and mean disease duration were 32.3 ± 11.4 and 6.9 ± 6.8 years respectively. Most patients (74.1%) received prior disease-modifying therapies. The mean ALCs decreased from 2190 to 1510/mm^3 (~30% decrease) over a mean duration of 11.7 ± 5.86 months. Among patients who had at least two follow-up ALCs, lymphopenia was seen in 22.2% of patients. Grade 1 and 2 ALCs were observed in 11.1% and 7.4% of patients, respectively, while 3.7% of the patients had grade 3 lymphopenia necessitating interruption or discontinuation of DMF.
Conclusion: ALC profiles in DMF-treated patients were generally stable throughout the observational period. The proportion of patients, who developed severe lymphopenia, was similar to figures reported in clinical trials. Further studies are needed to assess the time of ALC recovery in severely lymphopenic patients.

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The use of alemtuzumab in patients with multiple sclerosis in a clinical setting: Kuwait's experience

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Background: Alemtuzumab is an anti-CD52 monoclonal antibody which has demonstrated efficacy in clinical trials and has recently been approved for treatment of patients with multiple sclerosis (MS) in Kuwait.

Methods: Using the national Kuwait MS registry, patients with MS who received alemtuzumab and had at least 6-month follow-up were identified. Demographics, clinical and magnetic resonance imaging (MRI) characteristics, and adverse events were collected. The primary outcome is to examine the efficacy and safety of alemtuzumab treatment in a clinical setting. Patients' status pre- and post-treatment was compared using chi-square and Student's *t*-tests.
Results: A total of 20 patients were included of whom 60% ($n = 12$) were female. The mean age and disease duration of the cohort were 31.8 ± 6.3 and 11.2 ± 5.2 years, respectively. The cohort included 14 patients with relapsing and 6 with active progressive MS. Most patients (90%) received prior disease-modifying therapies, while two naive patients received alemtuzumab due to their aggressive and highly active disease. The mean follow-up duration after the first infusion of alemtuzumab was 17.7 ± 7.1 months with 55% of the patients receiving two courses of alemtuzumab. The annualized relapse rate was significantly reduced (0.1 vs 1.1; $p < 0.001$), and the mean Expanded Disability Status Scale (EDSS) score at last visit improved when compared to pre-treatment scores (3.6 ± 2.4 vs 4.2 ± 1.9; $p = 0.001$). Only one patient continued to have persistent gadolinium-enhancing lesion on follow-up MRI. Majority of patients ($n = 17$) developed mild to moderate infusion-related reaction and three patients developed autoimmune thyroiditis, two of whom were subclinical.
Conclusion: The effectiveness of alemtuzumab therapy in clinical practice mirrors the results seen in pivotal clinical trials. Autoimmune thyroiditis is common necessitating prompt vigilance and identification.

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Early changes in the normal appearing white matter in patients with acute optic neuritis using diffusion tractography

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Background: Acute optic neuritis is the initial presentation in approximately 20% of cases of multiple sclerosis. Conventional magnetic resonance imaging (MRI) is sensitive for detecting brain lesions in most, but not all patients. Diffusion tractography provides information about the diffusion properties of water molecules and microstructural tissue changes not visible on conventional MRI.
Methods: This study included 26 patients with acute demyelinating optic neuritis and 10 age- and sex-matched healthy controls. All patients had normal conventional MRI brain. Diffusion MRI tractography was done to all patients within the first 3 days of onset. Diffusion parameters including apparent diffusion coefficient and fractional anisotropy were measured in different regions of white matter.
Results: Compared with controls, all patients showed significant decreased mean fractional anisotropy in the normal appearing white matter ($p < 0.05$). We found no significant difference in the apparent diffusion coefficient (ADC) values in patients when compared with the control group ($p > 0.05$). The study showed that fraction anisotropy (FA) is more sensitive than ADC for detection of white-matter abnormalities in demyelinating optic neuritis patients. Corpus callosum is an early site for development of white-matter anisotropy changes in patients with optic neuritis.
Conclusion: Diffusion tractography seems to provide available means of indirectly detecting subtle changes in the normal appearing white matter not visible on the conventional brain MRI. FA is more sensitive than ADC to detect white-matter damage in demyelinating optic neuritis patients.

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Bilateral invasive breast carcinoma complicating treatment with natalizumab for multiple sclerosis

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Background: Natalizumab (NTZ) is a disease-modifying therapy (DMT), which was approved as a second-line treatment for patients with relapsing-remitting multiple sclerosis (RRMS) who are uncontrolled with first-line therapies, or as a first-line treatment for highly active RRMS.
Case report: A 49-year-old lady was diagnosed with MS in 2004; she was treated initially with interferon-beta-1-a. Because of the continued disease activity, treatment was upgraded to NTZ. There was no evidence of disease activity following the upgrade. She received NTZ monthly infusions for 6 years. She has been regularly assessed since 2011 for bilateral breast intra-ductal papilloma. In January 2017, mammogram and breast ultrasound were highly suspicious of malignancy. NTZ was discontinued. Biopsy showed invasive ductal carcinoma in both breasts.
Discussion: The risk of cancer in patients with MS is thought to be low. However, with the increasing use of immunomodulators, the risk becomes more concerning. We continue to learn more about the long-term effects of treatment with NTZ. Many papers in the literature describe the incidence of variable malignancies after treatment with NTZ for variable durations. Breast cancer has been seen in patients on NTZ, but thought to not exceed the rate in general population. However, there is no further specification of the type of cancer or prognosis. The mechanism of action of NTZ might explain why breast cancer could be of a concern, knowing that integrin expression is reduced in breast cancer cells. It is reasonable to think that NTZ contributed to the malignant transformation of the benign breast lesions. In a risk evaluation study for malignant transformation of breast intraductal papilloma, only 1.1% were at risk.
Conclusion: We are raising the possibility of a higher risk of breast cancer in patients treated with NTZ. Although an association cannot yet be established, we propose that patients treated with NTZ need to be monitored carefully for the development of breast cancer, particularly those with existing benign intraductal papilloma. The latter group might be better off treated with a different DMT. Alternatively, they could undergo a prophylactic surgical resection.

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Modified Brief International Cognitive Assessment for Multiple Sclerosis (mBICAMS): Toward validating the first Arabic version

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Background: Cognitive performance is an indicator of disease progression in multiple sclerosis (MS). The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) psychometric characteristics were not established in Arabic-speaking populations. The objective of this study was to validate and provide normative data for the BICAMS in Arabic.
Methods: In this cross-sectional study, we will administer the modified BICAMS (mBICAMS) to 184 healthy subjects with no history of neurological disorders, traumatic brain injury, psychiatric disorders, and cognitive impairment, age 16–90 years, and 50 patients with MS in addition to screening to exclude participants with depression and/or cognitive impairment. mBICAMS consists of three tests: Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test — Revised (BVMTR), and a newly developed Verbal Memory Arabic Test (VMAT).
Results: To date, 93 participants were screened (10 excluded and 5 participants dropped out). In all, 77 healthy subjects (43 females and 34 males) and 1 patient with MS completed the study, and retest was performed on 45 of these subjects after 21 days (mean age 29.5 ± 10.8 years). SDMT yielded 61.38 ± 8.96 correct answers (test–retest r = 0.64). On the VMAT, mean number of words recalled on the first five learning trials was 10.99 ± 1.49, short delay recall 11.23 ± 2.29, cued recall 11.53 ± 2.15, long delay recall 11.88 ± 2.29, cued recall 11.99 ± 2.24, and recognition trial 43.45 ± 1.98 out of 45 words. VMAT showed acceptable test–retest reliability; r = 0.43. On the BVMT-R, participants scored 5.42 ± 2.42 on trial 1, 8.75 ± 2.42 on trial 2, and 10.42 ± 1.88 on trial 3 (test–retest Cohen's d = 1.15).
Conclusion: Recruitment and data collection are ongoing. Validating the mBICAMS allows accurate clinical use and research utilizations of these measures in the Arab world.

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Development of the Verbal Memory Arabic Test (VMAT)

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Background: Verbal memory assessment requires the memorization of words across several trials and recalling these words with and without aid across time. This testing type is integral to neuropsychological assessment and is widely used in clinical and research settings. However, verbal memory tests are often translated from existing Western tools
a process that poses serious cultural and psychometric problems when interpreting the finding. Our study aimed to develop a test that is culturally and psychometrically robust to memory impairment among Arabic-speaking people.
Methods: In order to identify 15 Arabic words that are culturally and linguistically appropriate, we recruited 77 normal adults from across Lebanon and asked them to generate words for seven semantic categories.
Results: We collected approximately 133 Arabic words per category, selected those with low to medium frequency, and further selected words based on 11 conceptual criteria. The most appropriate words constructed the primary memory list of 15 words (List A), and two lists served as interference (List B) and recognition items. The final version of the Verbal Memory Arabic Test (VMAT) comprised five trials of List A, followed by interference list, then immediate recall of List A with and without semantic cues, then delayed recall after 15 minutes, and finally a recognition trial.
Conclusion: The VMAT is the first neuropsychological tool developed intentionally as a culturally and linguistically valid verbal memory test in Arabic. The next step is to provide normative data and evidence of its validity and reliability on 184 normal adults (older than 16 years), 50 patients with multiple sclerosis, and other special populations.

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Validation of MusiQoL among Arabic-speaking patients with MS treated with high-dose INF-β 1a SC injection new formulation

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Background: Validated quality-of-life (QOL) tools are not available for Arabic-speaking patients with multiple sclerosis (MS). 36-Item Short-Form (SF-36) and MusiQoL have been validated for other languages. The objective of this study was to prospectively assess and correlate MusiQoL with disease activity and progression among Arabic-speaking patients with MS treated with interferon beta-1 a subcutaneous (INF-β 1a SC) injection new formulation over 12 months.
Methods: The subjects comprised a prospective multinational, multicenter cohort study of Arabic-speaking patients with MS treated with rebif new formulation (RNF) for at least 6 months prior to entering the study. Their clinical parameters and QOL were assessed at baseline and by follow-up after 6and 12 months. Changes in MusiQoL total and subdomain scores were compared using the paired T-test. QOL changes from baseline and important parameters in QOL were correlated using Pearson and point biserial methods.
Results: In all, 439 subjects from four Arabic-speaking countries were included. Their average age was 32.44 (±0.34) years, 71.5% were female, and 63.1% were educated to university level or above. The subjects had an average MS duration of 4.13 (±0.12) years, an average age at first attack of 27.35 (±0.26) years, and baseline Expanded Disability Status Scale (EDSS) of 2.05 ± 0.04. Overall QOL measured using SF-36 remained generally unchanged over time (p = 0.215). However, QOL change overtime measured using MusiQoL was statistically significant (p = 0.00015). Several aspects of subjects' QOL including daily living activities, physical well-being, symptoms, and coping improved. Sentimental and sexual life decreased overtime (p = 0.0072).

Conclusion: The study suggests that the use of MusiQoL among Arabic-speaking patients with MS is a valid tool and may capture changes in several aspects of their clinical status over 12 months. Periodic assessment of QOL is recommended for management of patients with MS.

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Biotinidase deficiency mimicking seronegative neuromyelitis optica: Initially manifesting symptoms in adulthood

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Background: Young children with untreated biotinidase deficiency (BD) may manifest variable symptoms based on their age of presentation. Older children, adolescents, and young adults may disclose predominant neurological deficits including para- or quadriparesis and visual loss.
Methods: We report a late-onset BD in a young adult who mimicked seronegative neuromyelitis optica.
Results: A 26-year-old man manifested as a disabling extensive cervical myelopathy and bilateral optic neuropathy, mimicking the findings of seronegative neuromyelitis optica. Neuroimaging was characterized by a magnetic resonance imaging (MRI) with T2/ fluid attenuated inversion recovery (FLAIR) hyper-intensity involving a long segment of the cervical spinal cord (bulbospinal junction-D2 segment) and bilateral optic nerves with moderately severe prolongation of P100 latency and moderate generalized brain atrophy. He was finally shown to have profound late-onset autosomal recessive BD with one copy inherited from either parent. He improved partially by oral biotin therapy.
Conclusion: This case record stresses the necessity to include BD as one of the mimickers in the differential diagnosis of patients with extensive myelopathy and/or bilateral optic neuropathy thus simulating seronegative neuromyelitis optica. This report supports the global newborn screening for this disorder.

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The application of stem cells in multiple sclerosis: An overview of open labels and ongoing studies

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Background: Mesenchymal stem cells' (MSCs) therapy emerges as a potential new hope for patients with multiple sclerosis (MS).
Methods: We have reviewed the published and on-going clinical trials that have tried MSC for treating MS that have been registered in the clinical trial section of the PubMed or EMBASE.
Results: A total of 114 patients were enrolled in 11 cell-base studies with encouraging results. About 62% had clinical improvement, 22% had a stable course, and 16% had a worsening course. Nine on-going trials will be done as double-blind studies; however, the remaining 10 studies are open label. Totally, from early registration of these studies in 2007 since completion of all studies in 2018, after about 11 years, 446 patients will be evaluated. Unfortunately, the enrollment criteria were clearly defined in only 11 studies and sadly 6 of them have a similar initial Expanded Disability Status Scale (EDSS) and final outcome evaluation tolls. In other words, at the end of these studies we will have only 124 patients enrolled in a similar referable study which would be unreasonable data for a good conclusion worldwide.
Conclusion: The cell-based therapies are safe and a reasonable therapeutic approach for progressive MS. Despite the good early results of MSC therapy in MS, it seems that the worldwide fashion about cell therapy in all parts of the world is so slow.

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Multiple sclerosis mimickers on initial presentation: Frequency, type, and predictors

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Background: The aim of this study is to explore the frequency, type, and predictors of multiple sclerosis (MS) mimickers among patients referred with a recent diagnosis of MS to two specialized MS centers in the Middle East.
Methods: This is a retrospective review of a prospectively followed cohort of patients with MS at two university specialized MS centers. All patients referred for MS were included. The final diagnosis was recorded, and demographic, clinical, laboratory, electrophysiological, and radiological variables were collected.
Results: A total of 554 patients were included in this study, of which 431 were referred for diagnostic confirmation. The final diagnosis of MS was confirmed in 300 (70%), while 114 (26%) turned out to have an alternative diagnosis and 15 (3.5%) fulfilled criteria for radiologically isolated syndrome (RIS). The most common alternative diagnoses were psychogenic (16.3%), non-specific magnetic resonance imaging (MRI) white-matter lesions (14.7%), neuromyelitis optica (NMO) (9.5%), migraine (8.6%), and systemic autoimmune disorders (8.6%). The strongest predictors of a final diagnosis of MS were as follows: younger age, presence of oligoclonal bands in the cerebrospinal fluid (CSF), periventricular, corpus callosum, spinal ($p < 0.0001$), or enhancing lesions ($p < 0.005$) on MRI.
Conclusion: Our study shows that 30% of patients referred for a suspicion of MS end up with a different diagnosis. The most common mimickers of MS in the Middle East are not different from what has been described in the Western countries. Age, MRI, and CSF findings can help with the differential diagnosis.

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Safety and efficacy of rituximab in multiple sclerosis: A retrospective observational study

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Background: To evaluate the efficacy and safety of rituximab in multiple sclerosis (MS) in a clinical practice setting.
Methods: Clinical data of adult patients with MS treated with off-label rituximab at Nehme and Therese Tohme MS center in Lebanon between March 2008 and April 2017 were retrospectively collected from medical charts. The main efficacy outcomes were proportion of patients free from relapses, annualized relapse rate (ARR), disability progression as measured by Expanded Disability Status Scale (EDSS), and magnetic resonance imaging (MRI) activity. Adverse events (AEs) were also recorded.
Results: A total of 64 rituximab-treated patients were included: 45 relapsing–remitting MS (RRMS) and 19 progressive MS ($n = 12$ secondary progressive MS (SPMS), $n = 1$ primary progressive MS (PPMS), and $n = 2$ relapsing-progressive MS (RPMS)). Patients were treated with 1000 or 2000 mg rituximab intravenous (IV) every 6–12 months for a mean duration of 31 ± 29 months. The subjects were 70.3% females with a mean age of 41.2 ± 12.8 years and mean disease duration of 7.7 ± 6.5 years. During treatment, the ARR decreased from 1.2 at baseline to 0.09 in patients with RRMS and from 0.3 to 0 in patients with progressive MS. The mean EDSS remained unchanged in RRMS and increased by 1.8 in patients with progressive disease. Between baseline and last follow-up, the percent of patients free from any new MRI lesions increased from 16% to 89% in the RRMS group and from 47% to 100% in the progressive group. Infusion-related AEs occurred during 6.5% of infusions and were all mild. A total of 24 AEs (37.5%) were recorded. Two of our rituximab-treated patients experienced serious AEs requiring surgical interventions: pyoderma gangrenosum vaginalis with perianal abscess and fistula, and increase in the size of a benign Grade I meningioma. No case of progressive multifocal leukoencephalopathy was detected.
Conclusion: Rituximab was well-tolerated and effective in reducing relapse rate and stabilizing disease in relapsing–remitting and patients with progressive MS in our real-world clinical practice setting. Its efficacy persists with continued treatment and is similar to that reported in a recent cohort in Sweden.

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Rebound syndrome after teriflunomide cessation in a patient with multiple sclerosis

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Background: We report a case of relapsing–remitting multiple sclerosis (RRMS) with severe rebound syndrome (RS) 12 weeks following discontinuation of teriflunomide therapy.
Case report: This is a case of a 38-year-old woman with RRMS of 9-year duration. She was diagnosed with RRMS in May 2008 and was started on interferon-beta-1a 44 μg subcutaneously three times a week. She developed a second relapse in 2009 with bilateral lower extremities' numbness and an increase in her Expanded Disability Status Scale (EDSS) to 3.0. A new brain magnetic resonance imaging (MRI) revealed one new lesion in the right temporal lobe but no evidence of enhancement. Her EDSS score improved to 1.5 after receiving a course of high-dose intravenous (IV) steroids, and she had no further relapses or new lesions on her annual brain MRIs until November 2015 when she was switched to teriflunomide due to persistent flu-like symptoms and injection site reactions. Few months later, she developed significant side effects on teriflunomide including menorrhagia, severe and persistent hair loss, and gingival bleeding leading to discontinuation of teriflunomide in October 2016. She decided to stay off treatment and in January 2017 developed right lower facial numbness, bilateral below-knee numbness, and gait imbalance with worsening of her EDSS to 3.5. She received a 5-day course of IV methylprednisolone but showed minimal improvement unlike her previous relapses. A month later, her condition worsened with increased lower extremities' numbness and weakness. Her EDSS increased to 6 and she was unable to walk without support. An urgent brain and spine MRIs were obtained which showed multiple new lesions with more than 11 ring enhancing lesions as compared to the last MRI performed in October 2016. Additional serological and cerebrospinal fluid (CSF) studies were obtained to rule out any other infectious or inflammatory disorders but were all negative. Her symptoms improved significantly after a second course of IV steroids and her EDSS decreased to 1.5 by March 2017. She was kept on oral prednisone 60 mg daily for 2 weeks and then started on rituximab at a dose of 2000 mg given in two doses separated by 2 weeks.
Conclusion: We report a patient with severe disease reactivation 12 weeks after stopping teriflunomide, consistent with the definition of RS. To the best of our knowledge, this is the first report of RS following discontinuation of teriflunomide.

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Efficacy and safety of natalizumab extended interval dosing

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Background: Natalizumab is highly effective in multiple sclerosis (MS) but carries the risk of progressive multifocal leukoencephalopathy (PML). It is postulated that extending the dosing interval from 4 to 5–8 weeks might decrease this risk by decreasing the α4 integrin saturation on the surface of mononuclear cells. The aim of this study was to assess the effect of extended interval dosing (EID) on the therapeutic efficacy of natalizumab.
Methods: We reviewed all patients treated in our MS center with natalizumab for at least 6 months using EID. A total of 55 patients were shifted after an initial treatment period at standard interval dosing (SID) to an EID ranging from 5 to 8 weeks. All patients had a baseline magnetic resonance imaging (MRI) before initiating therapy and a follow-up MRI every 6 months thereafter.
Results: The mean treatment duration on SID and EID was 16.7 ± 13.0 and 9.1 ± 6.4 months, respectively. The mean age of our patients was 35.9 ± 11.7 years, mean disease duration 5.4 ± 6.4 years, 79.5% were females, and 94.5% had relapsing–remitting MS as opposed to 5.5% with secondary progressive MS. Before initiating therapy, annualized relapse rate (ARR) was 0.83, mean EDSS 2.52 ± 1.5, and 63.6% of patients were JCV antibody

positive (antibody index ≤ 0.9 in 72.5% and ≥1.5 in 25.5% of cases). By the end of SID and EID treatment, 92.7% and 93.3% of patients were free of relapses (p = not significant (NS)) and the ARR decreased to 0.05 and 0.06, respectively (p = NS). The mean Expanded Disability Status Scale (EDSS) at the end of SID and EID periods was 1.7 ± 1.4 and 1.8 ± 1.3, respectively (p = NS). A total of 72.7% and 92.7% of patients were free of any new T2 or enhancing lesions on MRI during the SID and EID periods, respectively (p = 0.011). It is of note that in the SID group the baseline MRI was performed before starting natalizumab. The overall incidence of adverse events was 51% versus 31% during SID and EID periods, respectively. Specifically, the rate of infections was higher during SID compared to EID (42% vs 20%). There were no cases of PML.

Conclusion: In patients treated with natalizumab, shifting from SID to EID has no negative effect on efficacy as evidenced by relapse rate, disability progression, and MRI activity. The EID regimen is associated with a lower rate of infections and might potentially decrease the risk of PML.

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The Bayesian Risk Estimate for MS at Onset (BREMSO) correlates with cognitive and physical disability in patients with early multiple sclerosis

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Background: Prevention of long-term disability is the goal of therapeutic intervention in relapsing–remitting multiple sclerosis (RRMS). The Bayesian Risk Estimate for MS at Onset (BREMSO) was designed to give an individual risk score predicting disease evolution into secondary progressive MS (SPMS). The aim of this study is to investigate whether BREMSO correlates with physical disability, cognitive dysfunction, and regional brain atrophy during the early disease course.

Methods: We investigated 100 patients with RRMS or clinically isolated syndrome (CIS) enrolled in the AUBMC Multiple Sclerosis Interdisciplinary Research (AMIR) study, with at least 2 years of follow-up and disease duration of less than 6 years. BREMSO score was calculated for all participants at disease onset. At each visit, cognitive function was assessed using the Symbol Digit Modalities Test (SDMT) and physical disability using the Multiple Sclerosis Severity Score (MSSS), Timed 25-Foot Walk Test (T25-FW), and nine-Hole Peg Test (9-HPT). Of the 100 patients, 30 had a baseline magnetic resonance imaging (MRI) performed at the radiology department of the AUBMC. 3DT1 with gadolinium injection and three-dimensional fluid attenuated inversion recovery (3DFLAIR) images were acquired. The intracranial volume (ICV) as well as the subcortical gray-matter structures and the corpus callosum (CC) were automatically segmented and their volumes measured.

Results: The mean (standard deviation (SD)) age was 28.1 (11.19) years, MSSS 3.17 (2.36), and disease duration was 2.4 (1.78) years. In multivariate linear regression analyses, controlling for age and education, the BREMSO score correlated negatively with SDMT at visit 1 ($\beta = -0.33$ $p = 0.019$), visit 2 ($\beta = -0.34$ $p = 0.017$), and visit 3 ($\beta = -0.34$ $p = 0.014$). BREMSO correlated positively with MSSS at visit 1 ($r = 0.38$, $p = 0.006$), visit 2 ($r = 0.47$, $p < 0.0001$), and visit 3 ($r = 0.42$, $p = 0.002$), but did not correlate with T25-FW and 9-HPT. MRI results showed a negative correlation between the BREMSO score and the CC volume at baseline ($p < 0.03$). No correlation was found between the BREMSO score and the intracranial volume and the subcortical gray-matter structures' volume. This can be due to the small sample size or short interval follow-up.

Conclusion: The BREMSO score is directly correlated not just with the physical progression of the disease (MSSS) but also with the cognitive disability (SDMT and CC volume measurements) in early MS. Future studies might incorporate MRI measures into the BREMSO score increasing the sensitivity and specificity of this score.

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Correlation of fatigue with cognitive and physical disability using clinical outcomes and MRI measurements

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Background: Fatigue is an underestimated symptom affecting up to 95% of patients with multiple sclerosis (MS). It does not only exacerbate impairment but also affects a patient's sense of control over the illness. In order to help patients cope with this disabling but treatable aspect of MS, it is necessary to understand the correlation between fatigue domains, cognitive functioning, and physical ability.

Methods: Adult patients with MS diagnosed as relapsing–remitting (RRMS) or progressive were clinically evaluated. The Modified Fatigue Impact Scale (MFIS) was administered to both MS and healthy age- and sex-matched control subjects. Processing speed was assessed using the Symbol Digit Modality Test (SDMT), and global brain atrophy was evaluated using magnetic resonance imaging (MRI) examinations. 3DT1 and three-dimensional fluid attenuated inversion recovery (3D-FLAIR) images were acquired and processed. Intracranial volume (ICV) and subcortical gray matter structures, lateral ventricles, and corpus callosum were segmented and their volumes measured using the volBrain pipeline (http://volbrain.upv.es) and the SIENAX tool in FSL. Univariate analysis was performed to explore differences between subjects with and without fatigue. Multivariate analysis controlling for age, gender, education level, Expanded Disability Status Scale (EDSS), disease duration, clinical depression, and MS type and treatment was performed to see the correlations between fatigue and the different variables.

Results: One-hundred-and-thirteen patients with MS with mean disease duration of 8.6 years and 57 healthy subjects were recruited. Significant fatigue was seen in 32.3% of patients with MS and 6.2% of controls. Among fatigued MS participants, 66% and 75% had physical and cognitive fatigue, respectively. Multivariate analysis showed that SDMT correlated negatively with fatigue ($p = 0.001$, odds ratio (OR) = 0.88), more specifically with its cognitive domain ($p = 0.003$, OR = 0.9). In addition, physical fatigue positively correlated with EDSS ($p = 0.04$, OR = 1.4), particularly with the pyramidal Functional Systems (FS) score ($p = 0.031$, OR = 2.5). In multivariable linear regression and

adjusting for age, disease duration, EDSS, and depression, there was a negative correlation between MFIS scores and ICV ($\beta = -0.54$, $p < 0.0001$) and a positive correlation with the volume of lateral ventricles ($\beta = 0.37$, $p = 0.006$) and all-ventricular volume ($\beta = 0.35$, $p = 0.007$).
Conclusion: There is an association between cognitive fatigue and SDMT, as well as physical fatigue with EDSS pyramidal FS score. There is also an association between cognitive and physical fatigue and brain atrophy.

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Fatigue evaluation in multiple sclerosis

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Background: Several studies showed that fatigue is a symptom independent of the neurological deficit intensity in multiple sclerosis (MS). The objective of our study was to evaluate the impact of various clinical aspects of this overwhelming tiredness, known as fatigue, in the daily life of patients with MS.
Methods: This is a cohort study of 68 patients with MS whose clinical and epidemiological characteristics were studied. We evaluated the fatigue and its impact on the cognitive, physical, and psychosocial dimensions, by the Fatigue Impact Scale (FIS) and its short version (Modified Fatigue Impact Scale (MFIS)). Analysis was performed by SPSS version 20 software.
Results: FIS and its various dimensions were strongly correlated with their MFIS equivalents ($r = 0.97$, $p < 0.001$). Fatigue (MFIS > 38) was present in 45 patients (66.2%). It was significantly correlated with high Expanded Disability Status Scale (EDSS; $r = 0.36$; $p < 0.001$), advanced age, and long duration of illness. Fatigue was more frequent in the progressive (100%) than in the relapsing–remitting form (65%, $p > 0.05$).
Conclusion: The significant correlation between FIS and MFIS gives the MFIS a high predictive value. Thus, MFIS can fully replace the long version. Fatigue assessment should be an integral part of MS management.

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The relationship between demographics of patients with MS and the utilization of services provided

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Background: Multiple sclerosis (MS) is a disabling life-long disease. It is associated with burden on the health system and patient's life including the economic impacts especially on the young patient population. These impacts have not been fully evaluated in the Middle East and North Africa (MENA) region though international studies have been conducted to determine the causes, incidence, associated risk factors, costs, and its effect on patients with MS.
Methods: This study is a descriptive population-based study using medical records database system Malaffi at Mafraq Hospital. The study protocol was reviewed and approved by the Mafraq Research Ethics Committee. All patients with a diagnosis of MS who visited the outpatient and inpatient settings in the hospital from January 2011 to December 2016 were included. The study aimed at identifying the direct costs of MS disease arising from diagnosis, management, and treatment. Statistical analysis was carried out using STATA software. Data were collected for 109 patients who used the following services: clinic visits, medications, hospital admissions, emergency room visits, brain and spine magnetic resonance imaging (MRI), laboratory investigations (complete blood count (CBC), liver function tests (LFTs), and vitamin D) from 2010 to 2016, and sick leaves for the year 2016.
Results: A total of 109 patients of 26 different nationalities were identified. The mean age was 34 years (16–64 years). The demographics consisted of the following characteristics: (1) age: young group (up to 19 years) 5%, middle age group (20–50 years) 87%, and older group (more than 50 years) 8%; (2) nationalities: Emiratis (37.7%) and expats (62.3%); and (3) gender: female 68.3% and male 31.7%. The frequency of service usage per year is as follows: young age 123 accounting for 5.86%, middle age 1796 accounting for 85.56%, and older age 152 accounting for 7.24%. From geographical aspects, the Emiratis frequency of service usage was 43.64% and Expat's 56.36%. As for gender, the female service usage frequency was 68.75% versus 31.25% for the male frequency.
Conclusion: This study assessed the frequency of utilization of the medical services by patients with MS. In view of increasing awareness and natural rise in cost index, an increase in disease burden vis-a-vis expenditure is expected. More research is needed to establish a solid plan to minimize and contain the raising economic burden of this disease.

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Measles, rubella, and varicella zoster (MRZ) virus reaction in CSF of patients with multiple sclerosis compared to other CNS inflammatory disorders

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Background: The aim of this study was to investigate the specificity of measles, rubella, and varicella zoster (MRZ) virus reaction for multiple sclerosis (MS) and to compare it with the diagnostic value of oligoclonal bands (OCBs).
Methods: In this study, 158 samples (79 couples of cerebrospinal fluid (CSF)/serum) were collected from 79 individuals. Samples were analyzed for OCB using CSF isofocusing. Levels of total IgG and albumin were determined by nephelemetry for total IgG index calculation and Reiber diagram interpretation. MRZ viruses' specific IgG levels were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) for virus antibody determination in CSF and serum. The intrathecal synthesis of IgG to MRZ viruses was detected by calculation of the corresponding virus-specific antibody index (AI) according to Reiber's formula. MRZ reaction was considered as positive if at least two AIs were ≥1.5. Statistical analysis was performed using SPSS version 20 software.

Results: The MRZ reaction positivity in patients with MS was four times as frequent as in control group (65.5% vs 16.6%; $p < 0.001$). The specificity and sensitivity of this reaction for MS diagnosis were 83.3% and 65.5%, respectively. As expected, in MS group, each of the three specific AIs was found more frequently positive and each median index value was higher in comparison with non-MS group. However, the difference reached a statistical significance only for R and Z viruses. In addition, the RZ reaction was the most prevalent profile among bispecific positive reactions (12/19). Regarding MS group, MRZ reaction positivity was significantly associated with the presence of total IgG in Reiber diagram ($p < 0.001$). This association was preserved for R and Z viruses when considering each anti-viral reaction alone ($p < 0.001$ and $p = 0.001$, respectively). The AI values of these two viruses were correlated to the total IgG index. Interestingly, in OCB-negative MS subgroup, MRZ reaction was detected in 53% of patients with a specificity of 92.3% for the disease. Furthermore, in OCB-positive patients with MS, the number of bands detected in CSF by isofocusing test was correlated to the R-specific AI value. The median value of this AI was significantly higher in OCB-positive compared to OCB-negative MS group.
Conclusion: Our results confirm that MRZ reaction is overall the most specific CSF marker of MS disease and demonstrate its interest in diagnosing OCB-negative patients with MS, which underline its high potential as a relevant diagnostic marker in clinical practice. Especially, the R and Z reactions were found to be qualitatively and quantitatively correlated to the IS of total IgG. However, the poorly understood pathophysiological role of MRZ reaction may require further research.

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Insomnia and disability severity among patients with multiple sclerosis in Saudi Arabia

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Background: Sleep disturbance is common among patients with multiple sclerosis (MS). Patients are in a vicious circle where both their physical and mental state may depend on or lead to sleep disorders and many health problems such as physic disability. In this study, our objective was to assess the insomnia and disability severity among patients with MS.
Methods: This study was conducted among a sample of 598 patients with MS resident in five regions in Saudi Arabia and between 15 and 60 years of age. To assess participants' demographic characteristics, disease-related factors, detected depression and medication adherence, and their association with insomnia and disability severity, this survey was conducted among consenting participants by a self-administered questionnaire that involves four validated scores (Insomnia Severity Index (ISI), Patient Determined Disease Steps (PDDS), Patient Health Questionnaire-9 (PHQ-9), and Morisky score). We used SPSS version 22 to analyze the data by applying chi-square test and one-way analysis of variance (ANOVA) tests.
Results: About 35.8% of the responders were male and 64.2% were female. The mean age at the time of diagnosis was 26.1 (±7.9) years, and the mean disease duration was of 6.7 (±6.2) years. The mean number of attacks in the past 2 years was of 2 (±2) attacks. Among responders, 23.1% were suffering from moderate to severe insomnia, 11.4% were suffering from advanced disability, and 50.5% from major depression. A total of 59.9% had low adherence to MS treatment. Overall, demographic and the remaining studied variables were significantly associated with the level of insomnia and the level of disability.
Conclusion: Awareness programs should be conducted in order to improve quality of life of patients with MS and to prevent physical and mental health problems which are frequent in MS population.

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Treatment adherence and satisfaction among patients with multiple sclerosis, Saudi Arabia: Cross-sectional study

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Background: Multiple sclerosis (MS) is an unpredictable, inflammatory, chronic disease. Adherence to disease-modifying therapy (DMT) is necessary to achieve improvement in clinical benefit. The objective of this study was to examine the association between adherence to medication and treatment satisfaction in patients with MS living in Saudi.
Methods: A cross-sectional study was carried out to assess treatment satisfaction and DMT adherence in patients with MS recruited from outpatient clinics of tertiary hospitals of five regions (south, east, west, middle, and north) in KSA. All patients answered a questionnaire regarding their MS treatment satisfaction, and the common Morisky Medication Adherence Scale (MMAS-8) was used to assess patient adherence. Patient Determined Disease Steps (PDDS) was used to measure disability. Data were analyzed using descriptive statistics, Mann–Whitney test, Kruskal–Wallis test, and Spearman's coefficient correlation.
Results: Of the 598 patients with MS studied, 384 (64.2%) were female. In all, 310 (51.8%) were married. Mean age was 32.4 years (standard deviation (SD) = 8.4 years). Mean age at disease onset was 26.9 years (SD = 7.6 years). The mean duration of illness was 6.5 years; the mean number of admission was 1.4 times (SD = 1.7 times). Almost 60% had low adherence and 80% of causes were due to presence of attacks and side effects. The mean treatment of satisfaction was 76.2. Treatment satisfaction was positively correlated with DMT adherence ($r = 0.268$, $p = 0.000$) and negatively correlated with PDDS ($r = -0.232$, $p = 0.000$). No statistical correlation was found between PDDS and DMT adherence. Marital status and educational level were significantly associated with DMT adherence at a level of significance of 0.05.
Conclusion: The study concluded that patients with MS have low adherence because of the occurrence of attacks and side effects of DMT. Treatment satisfaction was not the only cause for DMT adherence. Most differences were found with respect to side effects and convenience of treatment.

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Quality-of-life assessment among patients with multiple sclerosis, Saudi Arabia: Cross-sectional study

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Background: Multiple sclerosis (MS) is an unpredictable, inflammatory, chronic, and potentially disabling neurological disease that is very common in young adults. The aim of this study is to determine the health-related quality of life (QoL) among patients with MS living in Saudi Arabia.
Methods: A cross-sectional study was carried out to assess the QoL of patients with MS. Patients were recruited from outpatient clinics of tertiary hospitals in five regions (south, east, west, middle, and north). Clinical and demographic data were collected, as well as information on patients' health status using the Arabic translation of the self-reporting 36-Item Short-Form (SF-36) questionnaire to assess QoL. The Patient Determined Disease Steps (PDDS) was used to measure disability. Data were analyzed using descriptive statistics, Mann–Whitney test, Kruskal–Wallis test, and Spearman's coefficient correlation.
Results: Of the 598 patients with MS studied, 384 (64.2%) were female. The mean score for males was higher than for females in all SF-36 QoL subscales. The mean age was 32.4 years (standard deviation (SD) = 8.4 years). The mean age at disease onset was 26.9 years (SD = 7.6 years). The mean duration of illness was 6.5 years; the mean number of admissions was 1.4 (SD = 1.7). Patients had the lowest scores in role motioning/emotional scale (mean = 42.6, SD = 43.3). The PDDS was negatively correlated with all SF-36 QoL subscales. SF-36 QoL for patients with MS differs significantly through demographic characteristics at a level of significance of 0.05.
Conclusion: This study concluded that patients with MS have a low QoL score and need more interests. Further development of the registration will provide access to the entire population of patients with MS and help comprehensively analyze the factors that affect the quality of their lives.

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Depression severity among patients with multiple sclerosis in Saudi Arabia

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Background: Our study aimed to assess depression severity among patients with multiple sclerosis (MS).
Methods: Our survey was carried out among a sample of 598 male (35.8%) and female (64.2%) patients with MS, Saudi and non-Saudi, from five different regions in KSA, between 15 and 60 years of age. We used a self-administered questionnaire that was developed specially for this study after consulting literature. The data were verified and analyzed using SPSS version 22.
Results: The mean patient age at the time of diagnosis was 26.1 (±7.9) years. The mean duration of the disease was 6.6 (±4.8) years. More than a quarter of patients (27.1%) were admitted in the last year. Our results revealed that 9.7% of participants had family history of MS, and 27.8% of respondents were suffering from different chronic diseases. A large proportion of patients were receiving drugs for MS (interferon beta (IFNβ) in 26.2% of patients). Among respondents, the majority (53.2%) were likely to have mild level of disability and mild depression severity (30.8%). Chi-squared test revealed significant relationship between level of disability and depression severity.
Conclusion: To cope with MS disease, patients should be educated and encouraged to adopt healthy habits and receive cognitive behavioral therapy helping them to ensure a better quality of life.

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Human leukocyte antigen (HLA) typing in Iraqi patient with multiple sclerosis (MS)

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Background: Multiple sclerosis is a demyelinating disease of the central nervous system with a presumed autoimmune etiology. The etiology of MS remains unclear, but according to current data the disease develops in genetically susceptible individuals and may require additional environmental triggers. The human leukocyte antigen (HLA) Class II alleles may have the strongest genetic effect in MS. Such associations have not been as clearly defined in many Arab populations, where even the frequencies of specific HLA antigens remain unclear. The study was designed to (1) study the HLA of Classes 1 and 2 in a multiple sclerosis (MS) population to verify the susceptibility for the disease in Iraqi Arab patients and (2) assess possible inter-relationships between HLA Class II antigens and clinical phenotypic variables in MS such as age at onset and gender.
Methods: Peripheral blood was collected from 100 patients with MS. McDonald's criteria were used for MS diagnosis. We supplied a questionnaire containing questions about parameters such as age, gender, ethnicity, positive family history, as well as subtype of MS; however, clinical parameters' estimation was carried out by 100 healthy individuals, without any autoimmune disease and familial history of MS, selected as control group. Controls were originally from the same geographical region and were matched with cases in ethnicity. HLA Class I (A, B) and Class II (DRB1*, DQB1*) antigens' tissue-typing was performed by polymerase chain reaction (PCR) amplification with sequence-specific primers (PCR-SSP) method in two groups of age- and sex-matched Iraqi subjects: (1) 75 patients with definite MS (52 relapsing–remitting and 23 relapsing-progressive) and (2) 100 healthy controls. The frequencies of specific HLA types were then compared between patients with controls, and in the former related to specified clinical parameters.
Results: As mentioned above, HLA Class I (A, B) and Class II (DRB1*, DQB1*) allele was evaluated among 100 patients with MS and 100 healthy age- and sex-matched individuals. The frequencies for Class I antigens—A*0901, A*0602, and B*0501—appeared higher with the presence of MS. For Class II antigens, frequencies of DRB1*0401, DRB1*1501, and DQB1*0502 were increased in patients with MS. HLA type DRB1*0401 was present

at higher frequencies in patients with a younger age at disease onset and in female patients.
Conclusion: This is the first report on HLA association with MS in Iraqi population using high-resolution sequence. There is a trend toward an association between HLA Class I antigens (A*0901, A*0602, B*0501) and Class II antigens (DRB1*0401, DRB1*1501, and DQB1*0502) and MS in Iraqi subjects. Additionally, it appeared that DRB1*0401 was more frequent in females and those with an early onset of the disease. This work is still in progress as we analyzed more patients with MS and normal control.

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Prevalence of transverse myelitis and neuromyelitis optica spectrum disorders in the United Arab Emirates: A retrospective, multi-center study

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Background: Transverse myelitis (TM) is an inflammatory syndrome of the spinal cord presenting with weakness, sensory loss, and bowel/bladder dysfunction. TM can occur as a monophasic condition or as part of a relapsing disease often associated with neuromyelitis optica spectrum disorders (NMOSDs). The incidence and prevalence of both TM and NMOSD in the Middle East is unknown.
Objective: To determine the prevalence and characteristics of TM and NMOSD in Abu Dhabi, United Arab Emirates.
Methods: This is a retrospective chart review conducted at four large government-run hospitals in Abu Dhabi Emirate between 2010 and 2016. Data collected included year of onset, presentation, laboratory results including anti-NMO/myelin oligodendrocyte glycoprotein (MOG) antibodies, and occurrence of any relapses.
Results: In all, 46 subjects were identified with either TM or NMOSD with 23 (50%) of them being national Emirati citizens. Within the overall group including pediatrics, the crude prevalence rate for monophasic TM was 1.0 and for NMOSD was 0.34/100,000. For the Emirati citizens age 20 years and above, the prevalence rate for monophasic TM was 2.46 and 1.76 for NMOSD. The whole group adult (≥20 years) prevalence rate was 1.00 for TM and 0.39 for NMOSD. The mean age was 42 ± 17.6 years with a mean age of onset of 37 ± 18 years and 54% were female. In the Emirati subgroup, 83% were female. Nine patients overall had a positive anti-NMO or anti-MOG antibody result, of which six of nine (66%) were Emirati citizens. Of the 30 subjects with available laboratory cerebrospinal fluid (CSF) analysis, 36.6% had elevated white blood counts (>5.0 × 106/L) and 43% had elevated protein levels. Of the 19 subjects with documentation of oligoclonal bands (OCBs) or IgG index, only 4 (21%) had either OCB or elevated IgG index.
Conclusion: This is one of the few studies describing the prevalence, epidemiology, and characteristics of TM and NMOSD among population in the Middle East demonstrating an adult prevalence rate for Emirati citizens of 2.46 for monophasic TM and 1.76 for NMOSD.

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Concurrent central and peripheral demyelination-CIDP and RRMS: A case report

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Background: Demyelinating diseases usually affect either the central nervous system (CNS) or peripheral nervous system (PNS). CNS and PNS demyelinating diseases rarely occur in same individual. There are few case reports about central and peripheral demyelination occurring simultaneously or sequentially.
Case report: This is the case of a 48-year-old lady who has been diagnosed with relapsing–remitting multiple sclerosis (RRMS) since age 27 years. She presented initially with unsteadiness of gait followed by motor and sensory symptoms over 2 years. She was initiated on interferon beta 1a injections, which was escalated to fingolimod due to clinical and radiological relapses. In May 2015, 20 years after the onset of MS, while on fingolimod, she noticed bilateral lower limb weakness, with examination revealing areflexic weakness with distal sensory loss. Magnetic resonance imaging (MRI) of brain and spine with contrast did not show any new lesion. Nerve conduction study showed demyelinating sensory and motor polyneuropathy, with conduction blocks affecting her lower limbs more than upper limbs. She was diagnosed as chronic inflammatory demyelinating polyneuropathy (CIDP), and intravenous (IV) immunoglobulin (IG) was started, following which her symptoms resolved. Currently, she is receiving monthly bolus IV IG with no more exacerbation of CIDP or MS for the last 2 years.
Conclusion: Association of CIDP with multiple sclerosis is rare; however, it needs to be recognized early, as it is a treatable disease. Thorough examination should be performed in patients with MS presenting with neurological deterioration to differentiate relapses from peripheral demyelination. Absence of MRI lesions should not be diagnosed as pseudo relapse unless other causes of neurological deterioration are ruled out.

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Highlights on cyclophosphamide effect in active relapsing–remitting multiple sclerosis

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Background: Cyclophosphamide (CYC) is an alkylating agent which produces immunosuppression and an anti-inflammatory immune deviation. CYC is used extensively in treating aggressive and rapidly progressive forms of multiple sclerosis (MS), with mixed results. The aim of this exploratory prospective study was to determine the effect of CYC therapy given to active form of patients with relapsing–remitting MS (RRMS) for better control of clinical disease activity regarding relapse rate, disease progression, and radiological outcome.
Methods: In all, 69 patients with active RRMS were treated and followed up for a period of 12 months. Totally, 22 patients

received monthly pulse doses of CYC with starting dose of 800 mg/m^2 with dose augmentation to induce leukopenia of 3000/mm^3 and/or lymphopenia of 800/mm^3 guided by complete blood picture 14 days after each dose plus 1 g of methylprednisolone; 23 patients received subcutaneous interferon beta-1a 44 IU three times weekly; and 24 patients received monthly methylprednisolone only. The primary outcome measure was annual relapse reduction, stabilization of disease progression (measured by Expanded Disability Status Scale (EDSS)), and decreased magnetic resonance imaging (MRI) activity measured by the presence of new T2 lesions and/or gadolinium-enhancing lesions at the end of study and during relapses as secondary outcome measure.
Results: At 12th month of therapy, CYC produced significant relapse reduction compared to pretreatment baseline state ($p < 0.001$) and to monthly methylprednisolone group ($p = 0.03$) with relative risk reduction equal to 80.2%. In comparison to interferon beta-1a, there was no significant difference ($p = 0.46$). CYC induced significant improvement in disability previously accumulated compared to pretreatment baseline state ($p < 0.001$), but no significant difference between groups ($p = 0.2$). Significant reduction in gadolinium-enhancing lesions ($p < 0.004$) was reported in CYC patients compared to pretreatment baseline state, but no significant difference between groups ($p = 0.06$).
Conclusion: CYC showed significant clinical and radiological beneficial effect on controlling RRMS activity.

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Outcomes of Iraqi patients with multiple sclerosis treated with natalizumab

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Background: Multiple sclerosis (MS) is a chronic heterogeneous demyelinating axonal and inflammatory disease involving the central nervous system (CNS) white matter with a possibility of gray-matter involvement in which the insulating covers of nerve cells in the brain and spinal cord are damaged. This damage disrupts the ability of parts of the nervous system to communicate, resulting in a wide range of signs and symptoms. Natalizumab is used to treat adults with relapsing forms of MS to slow the worsening of symptoms common in people with MS and to decrease the number of relapses.
Methods: This is a cross-sectional study that enrolled 72 patients. The study was conducted in Baghdad teaching hospital in MS clinic from April 2015 to December 2016. The medical charts of all patients with MS admitted to Baghdad hospital to receive natalizumab infusion were reviewed. Data about any new neurological symptoms, disability progression measured by Expanded Disability Status Scale (EDSS), and new lesions on brain magnetic resonance imaging (MRI) with contrast (T1, T2, three-dimensional fluid attenuated inversion recovery (FLAIR), T1 with contrast) were collected. The diagnosis of MS was made according to the 2010 McDonald's criteria.
Results: Mean age of patients was 32.5 ± 8.1 years, with a female-to-male ratio of 1.7:1. Half of the patients were unemployed, and 30% of them were working currently. Overall, 51 (70.8%) patients had no new clinical attacks. A total of 72.2% of the patients had no new MRI lesions. There was significant reduction in EDSS; however, despite this significant reduction in EDSS, it was modest (median change was 0.25, 5.88% reduction) that only 5.6% of the patients had decline in their EDSS. There was a strong inverse relationship between EDSS change and number of doses which indicate that as the number of doses increases there is a reduction in EDSS.
Conclusion: Our study provides evidence that natalizumab significantly reduces the progression of disability, the occurrence of clinical relapse, and the appearance of new MRI.

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Epstein–Barr virus antibodies in a sample of Egyptian patients with relapsing–remitting multiple sclerosis

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Background: An association between Epstein–Barr virus (EBV) and multiple sclerosis (MS) has always been postulated. This study aims to detect the association of EBV as a risk factor of MS in a sample of Egyptian patients and its relationship to the clinical and radiological features of the disease.
Methods: In all, 86 Egyptian patients with the diagnosis of relapsing–remitting MS (RRMS) were recruited consecutively from MS Unit of Neurology Department at Ain Shams University Hospital and were compared to 64 healthy age- and sex-matched controls in this case–control prospective observational study. Patients' medical history and general and neurological examination including assessment of the functional disability using Expanded Disability Status Scale (EDSS) were obtained, and all subjects underwent serum sampling for detection of the anti-EBV IgG antibodies using enzyme-linked immunosorbent assay (ELISA) technique.
Results: Data showed that 92.9% of the patients had positive anti-EBV antibodies compared to 30.3% of the controls ($p < 0.001$) detected. The seropositive patients had significantly longer duration of illness ($p = 0.024$), higher number of relapses ($p = 0.026$), and higher EDSS scores ($p = 0.001$). While EBV antibody titer was significantly directly correlated to the duration of illness ($p = 0.014$).
Conclusion: These data together with earlier reports strengthen the hypothesis that EBV infection or the immune response to EBV antigens has a potential role in pathogenesis of MS illness and progression of the disease.

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Human herpes virus-6 as a risk factor of relapsing and remitting multiple sclerosis in a sample of Egyptian patients

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Background: Multiple sclerosis (MS) is a chronic autoimmune illness of the central nervous system which is considered the most common non-traumatic cause of neurological disability in middle age. Numerous techniques have been used to investigate the possible association between human herpes virus-6 (HHV-6) and MS. This study aims to detect the possible association of HHV 6 as a risk factor of MS disease in a sample of Egyptian patients.
Methods: A total of 90 Egyptian patients were included in our sample from MS unit patients' records from the Neurology Department at Ain Shams University Hospital with relapsing–remitting MS (RRMS) type. In all, 60 healthy controls matching the patients in age and sex were added to the study for correlations. Patient's medical history and general and neurological examination including assessment of MS according to the Revised McDonald criteria for MS diagnosis and functional disability using Expanded Disability Status Scale (EDSS) were assessed at admission. All subjects underwent serum sampling for detection of anti-HHV-6 IgG using enzyme-linked immunosorbent assay (ELISA) technique.
Results: Highly significant correlation in the IgG response of patients with RRMS to antigen of HHV-6 compared to that of normal controls ($p < 0.001$) was detected. Other clinical determents for MS course and progression showed a high significant association between duration of illness of MS and the presence of HHV-6 IgG in serum ($p = 0.009$) and a significant association between the total number of relapses and presence of HHV-6 IgG in serum ($p = 0.011$).
Conclusion: Our data together with earlier reports strengthen the hypothesis that HHV-6 infection or the immune response to HHV-6 antigens has a potential etiological role in MS illness. Awareness of this relation between MS and HHV-6 infection might improve early diagnosis of MS and improve researches for curative treatment.

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Fulminant multiple sclerosis, what to do? Diagnostic approach and management options

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Background: Fulminant multiple sclerosis (MS) is the most aggressive type of MS, which typically leads to great disability and even death within weeks. It is usually monophasic and represents a medical emergency that calls for urgent management. Fulminant MS includes two variants, Marburg type and Balò concentric sclerosis. The Marburg type, which also called tumefactive MS, is characterized by tumor-like demyelinating brain lesions while the Balò subtype is characterized by concentric layers of alternate myelination and demyelination.
Methods: A systematic literature review has been done to identify the cases of fulminant MS. Our objectives were to evaluate the diagnostic strategies and therapeutic approach and to highlight the characteristic clinical, pathological, and radiological features of fulminant MS.
Results: (1) Pathological features: Balò's variant was characterized by alternate concentric layers of demyelination and preserved myelin. While the Marburg subtype was characterized by demyelination associated with profound inflammation, tissue destruction, necrosis, and macrophage infiltration. (2) Presentation: fulminant MS is more common in young and usually monophasic. The symptoms may start with fever in some cases followed by a decreased level of consciousness and focal neurological deficit. Seizure has also been reported. Peripheral nervous involvement has also been reported in some cases of Marburg subtype. (3) Magnetic resonance imaging (MRI) with contrast: the Marburg variant is characterized by large lesions of tumefactive demyelination with mass effect and incomplete ring enhancement, but rarely presented with disseminated small demyelinating lesion. Remyelination of affected areas is rare. While in Balò concentric sclerosis, round lesions with irregular concentric rings of low and high signal alternate to give the onion bulb appearance. Peripheral enhancement indicates active demyelination. It may also be associated with peripheral diffusion restriction.
Conclusion: Fulminant MS is a rare type of MS which has a grave prognosis especially if not diagnosed and treated promptly and appropriately. Other fulminant demyelinating disorders as well as viral encephalitis, progressive multifocal leukoencephalopathy (PML), high-grade gliomas, and lymphomas need to be excluded.

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Vitamin B12 and its impact on multiple sclerosis type and severity

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Background: Cyanocobalamin (vitamin B12) deficiency is considered an important multiple sclerosis (MS) mimic; this is due to the similarities clinically and pathophysiologically of both diseases, as both attack the myelin sheath of the nervous system. The study aimed to determine the association between vitamin B12 levels and MS type and severity.
Methods: This is a retrospective single-center study of patients seen at the specialized MS clinics. Data were obtained through the MS database for a total of 350 patients. Patients were divided into either relapsing–remitting MS (RRMS) or progressive MS (PRMS). Vitamin B12 values were obtained at the first visit and a cutoff value of 200 pg/mL or above was considered normal. The severity of MS was evaluated using the Extended Disability Status Scale (EDSS). Fisher's exact test was used to identify whether vitamin B12 levels distinguished between MS types. Local regression was used to assess the correlation between vitamin B12 levels and the EDSS.
Results: A total of 100 patients with MS had vitamin B12 levels (91 RRMS and 9 PRMS) with a 1:1.5 male-to-female ratio. B12 levels were below normal in 30 RRMS cases and 1 SPMS case ($p = 0.27$). Local regression showed an inverse relation between vitamin B12 levels and EDSS at the sub-therapeutic levels; this relation plateaued once the therapeutic levels were reached.
Conclusion: Low vitamin B12 levels were inversely correlated with MS disability measures but failed to distinguish between MS

types. The small sample size of PRMS was considered a limitation in our study. Future studies looking at the effects of vitamin B12 on MS severity are needed.

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Spectrum of primary headaches in multiple sclerosis

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Background: Headache is not considered as a symptom of multiple sclerosis (MS). However, several studies have shown a relationship between these two diseases.
Objective: To study the frequency, characteristics, and timing of primary headache in patients followed for MS.
Methods: This is a retrospective study including patients followed for MS in the Neurology Department at the Razi Hospital between July and December 2016. For each patient, we collected anamnestic, clinical, and radiological data. The information collected from the patients' medical records were placed on fact sheets and analyzed by Excel.
Results: In all, 50 patients were identified: 22 men and 28 women. The frequency of headache was present in 82%. Migraine headaches were present in 54%, tension in 39%, and trigeminal neuralgia in 6%. For migraine headaches, we noted 20% with aura and the remainder without aura. Cerebro-medullary imaging showed subcortical lesions in 62.5%, periventricular lesions in 92.5%, brain stem lesions in 65%, and medullary lesions in 65%. There was an exacerbation of headaches' frequency after the diagnosis of MS in 60%.
Conclusion: Most headaches during MS are migraine. They are more frequent in women than in men. There has been an increase in the frequency of migraine attacks during MS most likely due to inflammation. The predominant radiological lesions are periventricular which are most predictable of causing headache.

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Uhthoff phenomenon in multiple sclerosis in a Tunisian cohort

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Background: The Uhthoff phenomenon is common in multiple sclerosis (MS). Few studies have examined this phenomenon in Africa.
Objective: To evaluate the incidence and clinical characteristics of the Uhthoff phenomenon in Tunisian patients with MS.
Methods: We used a questionnaire for patients with MS followed in the Neurology Department at the Razi Hospital (Tunisia), from 1 October to 30 November 2016, concerning transient and brief neurological symptoms triggered and/or aggravated by an increase in body temperature. We have included patients with an Uhthoff phenomenon. Their symptoms were classified as motor (weakness, disturbance of balance), sensory (numbness, tingling, burning), visual (blurred vision, diplopia), and vesicosphincter (urinary incontinence).
Results: In all, 57 patients were included with an average age of 38.6 years. The Uhthoff phenomenon was noted in 61.4% of patients with predominant motor symptoms (71.4%) followed by visual symptoms (48.5%) and sensory symptoms (37.1%). About 22 patients had two or more types of symptoms. Symptoms occurred after 3–60 minutes (standard deviation (SD) = 18.3 minutes) and disappeared completely after 5 minutes to 3 hours (SD = 45.2 minutes). Walking was the primary trigger (62.8%).
Conclusion: The frequency of the Uhthoff phenomenon has not been studied in African countries. Indeed, our study has shown a high frequency according to Asia (48.1%) and Western (80%) countries. The main triggering factor is exercise as walking was most common in our study. Temperature-dependent central motor conduction blockage of partially demyelinated axons has been proposed as the main pathophysiological mechanism.